IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PACIRA PHARMACEUTICALS, INC., and PACIRA BIOSCIENCES, INC., Plaintiffs, v. EVENUS PHARMACEUTICALS LABORATORIES, INC., JIANGSU HENGRUI PHARMACEUTICALS CO., LTD., and FRESENIUS KABI USA, LLC, Defendants.	Civil Action No. 2:21-cv-19829 Civil Action No. 2:22-cv-00718 (consolidated) Assigned to: Judge Madeline Cox Arleo Magistrate Judge Jose R. Almonte

DEFENDANTS' PROPOSED POST-TRIAL FINDINGS OF FACT

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TABLE OF ABBREVIATIONS

ABBREVIATION	TERM
'336 Patent	U.S. Patent No. 11,179,336 (JTX-4126)
'348 Patent	U.S. Patent No. 11,426,348 (DTX-2152)
'400 application	U.S. Application No. 17/156,400
'486 Patent	U.S. Patent No. 11,311,486 (JTX-4133)
'494 Patent	U.S. Patent No. 11,278,494 (JTX-4130)
'495 Patent	U.S. Patent No. 11,033,495, the sole patent-in-suit (JTX-4121)
'691 Patent	U.S. Patent No. 11,452,691 (JTX-4140)
'727 Patent	U.S. Patent No. 11,357,727 (JTX-4009)
'838 Patent	U.S. Patent No. 9,585,838 (JTX-4089)
'904 Patent	U.S. Patent No. 11,304,904 (JTX-4131)
2018 EXPAREL® Label	FDA approved EXPAREL® with a twenty-four month shelf life and indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia (DTX-3115)

AAPS	American Association of Pharmaceutical Scientists
ANDA	Abbreviated New Drug Application
ANDA Products	the bupivacaine liposome injectable suspension products that are the subject of Jiangsu Hengrui's ANDA No. 214348
API	active pharmaceutical ingredient
Asserted Claim	claim 7 of the '495 Patent
DDS(s)	drug delivery system(s)
DEPC	1, 2-dierucoylphosphatidylcholine
DPPG	1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol)
DTX	Defendants' Trial Exhibit
FDA	U.S. Food and Drug Administration
ICH	International Council for Harmonisation
JTX	Joint Trial Exhibit
Knobbe	Knobbe Martens
LOD	limit of detection
LOQ	limit of quantification
Los Declaration	Declaration of Kathleen Los submitted on behalf of Pacira in support of the prosecution of the application leading to the '495 Patent on April 22, 2021 (DTX-2262)

Los Spreadsheet	named inventor Kathleen Los's compilation of data underlying the '495 Patent in an Excel spreadsheet (JTX-4037)
MPEP	Manual of Patent Examination Procedure
MVL(s)	multivesicular liposome(s)
NDA	New Drug Application
ND	not detected
NMT	not more than
Pacira or Plaintiffs	Pacira Pharmaceuticals, Inc. and Pacira BioSciences, Inc., collectively
PDR	Physician's Desk Reference
POSA	person of ordinary skill in the art
Prior Art EXPAREL® Product or prior art 45-liter EXPAREL®	Pacira's EXPAREL® Bupivacaine Liposome Injectable Suspension, commercially available, on sale, or publicly available before January 22, 2021, and manufactured by a 45-liter process
PTO, Tab 5	Joint Final Pretrial Order (D.I. 298), entered by the Court on January 4, 2024, Tab 5, Stipulation of Facts
PTX	Plaintiffs' Trial Exhibit
QC	Quality Control
RLD	reference listed drug
SCC	Science Center Campus

sNDA	Supplemental New Drug Application
Tr.	Trial Transcript
USPTO	U.S. Patent & Trademark Office
w/o/w	water-in-oil-in-water
w/o	water-in-oil

I. BACKGROUND

A. TIMELINE OF SELECTED EVENTS

1. EXPAREL® is an encapsulated multivesicular liposome ("MVL") suspension with bupivacaine as the active pharmaceutical ingredient ("API"), manufactured and marketed by Pacira. PTO Tab 5 ¶ 24; Tr. 74:21-24 (Hall), 386:5 (Schwendeman); DTX-3115.23-24; JTX-4205.19. EXPAREL® was initially approved by the U.S. Food & Drug Administration ("FDA") in October 2011. PTO Tab 5 ¶ 19; Tr. 91:14-15 (Hall).

2. As of EXPAREL®'s initial approval in October 2011 and continuing through the present day, Pacira has used a 45-liter manufacturing process to produce EXPAREL®. *See* Tr. 454:5-14 (Schwendeman), 91:14-21 (Hall); DTX-3109.

3. Between 2012 and January 22, 2021, Pacira manufactured and sold over 2500 batches of EXPAREL® using its 45-liter commercial-scale manufacturing process. Tr. 444:12-14, 454:5-14 (Schwendeman); DTX-3109; Tr. 91:14-21 (Hall); PTO Tab 5 ¶ 20 (confirming EXPAREL® has been commercially available in the United States since 2012).

4. From its launch in 2012 through the present day, EXPAREL® has generated billions of dollars in revenue for Pacira. *See* DTX-3116.10; Tr. 341:5-22 (Molloy). EXPAREL® is Pacira's highest-selling product, generating a majority of the company's revenue. DTX-3116.10; Tr. 341:16-18 (Molloy).

5. Starting in approximately 2013, Pacira began efforts to scale up its 45-liter commercial-scale manufacturing process into a 200-liter process, and ultimately installed a 200-liter production facility in Swindon, UK. Tr. 93:21-94:6, 99:17-18 (Hall).

6. By 2020, Pacira had completed installation of its 200-liter production facility, had finalized its 200-liter manufacturing process, and was preparing to seek the FDA's regulatory approval for the 200-liter Swindon facility. *See id.* at Tr. 104:12-17 (Hall).

7. In preparation for seeking the FDA's regulatory approval for the 200-liter Swindon facility, Pacira manufactured several batches of EXPAREL® using its proposed 200-liter process, including three "registration batches." *Id.* at Tr. 134:20-23 (Hall).

8. As of late 2020, Pacira only had a single patent listed in the Orange Book for EXPAREL®: U.S. Patent No. 9,585,838 ("'838 Patent"), which was going to expire in December 2021. Tr. 339:6-15 (Molloy); DTX-2019. The expiration of Pacira's last Orange Book-listed patent would have allowed for entry of generic competition to EXPAREL®. *Id.* at Tr. 339:11-340:1 (Molloy).

9. In late 2020, Pacira scientists started measuring various physical properties of three (3) of Pacira's 200-liter registration batches and comparing them to various 45-liter "reference batches." Tr. 178:17-19, 196:21-197:1 (Grigsby).

10. On January 22, 2021, Pacira filed the application leading to U.S. Patent No. 11,033,495 ("the '495 Patent"). JTX-4121.1. The '495 Patent issued on June 15, 2021. *Id.*

11. In 2020, prior to the issuance of the '495 Patent and before Pacira had even filed the patent application, Jiangsu Hengrui had manufactured batches of the ANDA Products. Tr. 541:13-21 (Schwendeman); JTX 4036.4; Tr. 305:13-306:23 (Karaborni). Jiangsu Hengrui could not have known about the '495 Patent when it developed its ANDA. *Id.*

B. BACKGROUND ON MULTIVESICULAR LIPOSOMES

12. A liposome is a small spherical structure composed of an external membrane and an internal liquid, or aqueous core. *See* Tr. 75:20-24 (Hall). The external membrane layer is composed of lipids, which are non-water soluble compounds, such as phospholipids, sphingomyelins, fatty acids, sterols, or cholesterols. Tr. 75:20-24 (Hall); 385:12-19 (Schwendeman). Phospholipids contain polar "heads" and hydrophobic fatty acid tails. Tr. 385:12-19 (Schwendeman). To form the lipid bilayer the polar heads are turned toward the aqueous media (either toward the internal media or toward the external media), while the hydrophobic tails are turned inside the bilayer to face each other. *Id.*

13. The internal liquid core can comprise a pharmaceutical ingredient in aqueous form, and hydrophobic drugs can be incorporated inside the lipid bilayer.

See Tr. 75:20-24 (Hall); 385:6-15 (Schwendeman). In this way, liposomes can act as drug delivery systems ("DDS") to deliver the pharmaceutical ingredient to a patient. Tr. 386:9-15 (Schwendeman).

14. Liposomes are categorized by their structures. *See* Tr. 385:20-25, 386:9-15 (Schwendeman); 596:23-597:9 (Yaman). For example, they can be unilamellar (having a single lipid layer, like a bubble or water balloon), multilamellar (having multiple lipid layers, like an onion), or multivesicular (having multiple chambers, like a pomegranate). Tr. 385:20-25, 386:9-15 (Schwendeman); 596:23-597:9 (Yaman).

C. THE PATENT-IN-SUIT

1. The Specification of the '495 Patent

15. The '495 Patent," entitled "Manufacturing of Bupivacaine Multivesicular Liposomes," issued on June 15, 2021, from U.S. Application No. 17/156,400 ("the '400 Application"), filed on January 22, 2021. JTX-4121.1; PTO Tab 5 ¶ 6. The face of the '495 Patent names Jeffrey S. Hall, David J. Turnbull, John J. Grigsby, Jr., Soroush M. Ardekani, Paige N. Davis, Louie D. Garcia, Stephanie M. Kurz, and Kathleen D. A. Los as the inventors. JTX-4121.1; PTO Tab 5 ¶ 6.

16. The subject matter of the '495 Patent relates to compositions of "bupivacaine encapsulated multivesicular liposomes . . . wherein the erucic acid

concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C for one month." JTX-4121.10 (2:19-67).

17. The specification of the '495 Patent provides the following Detailed Description:

> Embodiments of the present disclosure relate to new and improved commercial scale manufacturing processes for making bupivacaine encapsulated multivesicular liposomes (MVLs). The newly developed processes provide up to 5 folds increase in final product volume as compared to the current process used for the manufacturing of Exparel®, which is disclosed in U.S. Pat. No. 9,585,838 and is incorporated by reference in its entirety. The processes also allow for improved product operability. In addition, the improved and scaled up process also yields a more stabilized form of bupivacaine encapsulated MVLs, having less lipid degradation byproducts, increased internal pH, and increased lysine and dextrose encapsulation.

Id. at 4121.4 (4:26-40).

18. The specification of the '495 Patent states that the erucic acid concentration indicates that the "process described herein" "yields a more stabilized form of bupivacaine encapsulated MVLs, having less lipid degradation byproducts, increased internal pH, and increased lysine and dextrose encapsulation." JTX-4121.11. More specifically, the specification states the following:

> The bupivacaine MVLs produced by the process described herein have improved stability over the commercial Exparel® product. It was observed that the bupivacaine MVL particles produced by the process described herein have lower lipid hydrolysis byproducts compared to the

> commercial Exparel® product under the same incubation condition. In addition, the bupivacaine MVL particles produced by the process described herein has higher internal lysine and dextrose concentrations and more desirable internal pH, which may improve MVL particle strength during product transportation, as well as lipid membrane stability.

Id. The reference in the specification to a "compar[ison] to the commercial Exparel® product under the same incubation condition" refers to the data presented in Example 1 of the '495 Patent. JTX-4288.8 (Dai Tr. 93:1-7, 93:10).

19. The '495 Patent further states that "[t]he improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected." JTX-4121.20 (21:52-55).

20. Example 1 of the '495 Patent describes a "lipid hydrolysis analysis," and purports to provide erucic acid concentration data for three batches "prepared by the new process" and ten batches prepared using Pacira's "current commercial process." *Id.* at 4121.19 (20:29-37). Example 1 states that "erucic acid was used as the marker to measure the stability of the lipid membranes of the MVL particles," and that "[a]ll the samples were incubated at 25°C for 1 month, 2 months, 3 months and 6 months," after which "[e]rucic acid was detected using HPLC." *Id.* at 4121.19 (20:38-45).

21. The erucic acid concentration results for Example 1 are set forth in Table 1A of the '495 Patent, captioned "Erucic acid concentration in the bupivacaine MVLs as a functional [sic] of time":

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (μg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

Id. at 4121.19 (20:49-67).

22. For batches "prepared by the new process," individual batch data is provided for three batches, after incubation at 25° C for one month, two months, three months, and six months. *Id.* at 4121.19 (20:34, 20:49-66). For batches prepared using Pacira's "current commercial process," only average erucic acid concentration data is provided at the two-, three-, and six-month timepoints, and no data is provided for the 1-month timepoint. *Id.* at 4121.19 (20:37, 49-66). At the one-month timepoint for the reference samples, Table 1A lists only "n/a." *Id.* at 4121.19 (20:49-67).

23. Example 1 refers to, among other things, FIG. 3B. *Id.* at 4121.20 (21:34-41). Figure 3B is described as "a line chart showing erucic acid concentration as a function of incubation time at 25 °C. of the bupivacaine-MVL compositions prepared by the new process described herein as compared to those prepared by the existing commercial process." *Id.*; *see also id.* at 4121.11 (4:13-18).

24. Figure 3B of the '495 Patent is reproduced below:

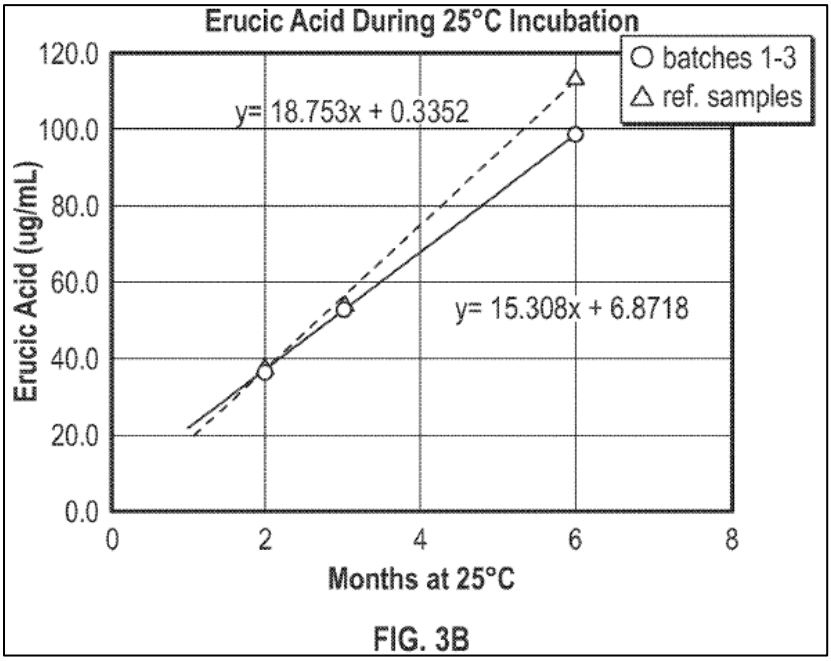


FIG. 3B

Id. at 4121.8.

25. According to the specification, the shelf life of the claimed product is "up to 2 years when stored at 2-8° C." *Id.* at 4121.12 (5:1-4).

2. Prosecution History of the '495 Patent

26. On March 25, 2021, examiner Jeffrey Washville rejected all pending claims of the application for the '495 Patent as obvious under 35 U.S.C. § 103, based

on the Camu and Li references (an issued U.S. patent and a published U.S. application, respectively). In this rejection, the Examiner set forth a *prima facie* case of obviousness, thereby shifting the burden to Pacira to respond by setting forth evidence of patentability. Tr. 637:22-639:19 (Slifer); Tr. 842:24-843:6, 862:3-864:12 (Godici); JTX-4001.2146-2152; DTX-3099.248.

27. On April 16, 2021, Examiner Washville and Dr. Jane Dai, outside counsel for Pacira, participated in an applicant-initiated telephone interview, discussing the obviousness rejection of claim 1. Tr. 638:21-640:17 (Slifer); JTX-4001.2167. The focus on claim 1 during the April 16, 2021 telephone interview was consistent with USPTO policy and procedure, as claim 1 was the only independent claim in the application at the time. Tr. 640:18-24 (Slifer); JTX-4001.2167.

28. This interview was summarized in the file history as follows:

> Discussed claim 1 rejection and Applicants argued that the combination does not teach the amount of erucic acid concentration ***after one month*** as ***the product by process is more stable than the cited art combination***. Applicants further argued that the process allows ***higher concentrations of bupivacaine*** as cited in claim 18. Office indicated that adding claims 17 and 18 to claim 1 and providing a declaration of why one skilled in the art would not expect the prior art to have the same ***claimed acid concentration*** should be allowable after a final search and consideration of the 3/12/2021 ids.

JTX-4001.2167 (emphases added).

29. During the April 16, 2021 telephone interview, Dr. Dai argued that the prior art did not teach the recited erucic acid concentration after one month, and that the new process allowed for a higher concentration of bupivacaine as recited in dependent claim 18. In response, the Examiner requested that claim 1 be amended to include the higher concentration of bupivacaine, and requested "a declaration of why one skilled in the art would not expect the prior art to have the same claimed acid concentration"—i.e., an erucic acid concentration of 23 µg/mL or less at the one-month timepoint. Tr. 640:25-641:24 (Slifer); JTX-4001.2167.

30. On April 22, 2021, Dr. Dai filed a response, attaching a declaration from named inventor Kathleen Los (the "Los Declaration"). Tr. 643:4-12 (Slifer); JTX-4001.2176. Dr. Dai's response stated the following:

> The present claims are directed to bupivacaine MVL compositions prepared by a newly developed commercial process. This new commercial process yields a bupivacaine MVL product with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, as measured by a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25° C. *See* Los Declaration at paragraph 4. The bupivacaine MVLs manufactured by the claimed process ha[ve] a target concentration of bupivacaine from about 12.6 mg/mL to about 17 .0 mg/mL and can be directly administered to a patient without further purification. *Id.* In addition, claim 1 recites, in part, "wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C for one month." These

> features are not expressly disclosed in either Camu or Li. Furthermore, the Office Action has not provided any evidence to demonstrate that these recited features are inherently present in either Camu or Li. As such, a *prima facie* case of obviousness has not been established at least because each and every claim limitation is not disclosed in the cited references.

JTX-4001.2176.

31. In the same April 22, 2021 submission, Dr. Dai amended claim 1 of the application to require a "target concentration" of bupivacaine of "from about 12.6 mg/mL to about 17.0 mg/mL," consistent with her telephone interview with the Examiner. *Id.* at 4001.2171; Tr. 641:25-643:3 (Slifer).

32. In her April 22, 2021 Applicant Remarks, Dr. Dai made arguments directed to the same two limitations discussed during the telephone interview: the one-month erucic acid limitation, and the purportedly higher concentration of bupivacaine. JTX-4001.2176 ("The bupivacaine MVLs manufactured by the claimed process has a target concentration from about 12.6 mg/mL to about 17.0 mg/mL . . . . In addition, instant claim 1 recites, in part, 'wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25°C for one month.' These features are not expressly disclosed in either Camu or Li."). Tr. 643:13-644:2 (Slifer). She did not mention that the claimed concentration of bupivacaine was the same as for prior-art EXPAREL, or that some of the 45-liter batches underlying the patent met the one-month erucic acid

limitation. Tr. 643:13-644:6 (Slifer); JTX-4001.2176. Dr. Dai also referenced purportedly "superior stability" of EXPAREL manufactured by the 200-liter process, as measured by erucic acid concentration "over a period of six months at 25°C," citing a declaration from Ms. Los in support. Tr. 644:7-21 (Slifer); JTX-4001.2176.

33. In context, Dr. Dai's statements regarding "improved stability" implied to the Examiner that the 200-liter EXPAREL batches had lower erucic acid concentration at the one-month timepoint of independent claim 1, as well as at the two-, three-, and six-month timepoints of the dependent claims. The Examiner specifically requested a declaration regarding the patentability of claim 1; therefore, it would have made no procedural sense to submit a declaration regarding "the trajectory of the erucic acid level over time, not an absolute number at an early timepoint." Tr. 645:2-9 (Slifer); JTX-4001.2176.

34. Consistent with the Examiner's request for a declaration from a person of ordinary skill in the art, Pacira submitted a declaration from Ms. Kathleen Los in support of Dr. Dai's arguments in her April 22, 2021 Applicant Remarks. Tr. 645:15-646:1 (Slifer); JTX-4001.2178. In Paragraph 4 of her Declaration, Ms. Los made statements regarding purportedly "improved stability" and the concentration of bupivacaine essentially identical to those in Dr. Dai's April 22, 2021 Applicant Remarks. Tr. 645:12-20 (Slifer); JTX-4001.2179.

35. Ms. Los stated in her declaration:

> The present application is directed to a 200L commercial scale manufacturing of bupivacaine multivesicular liposomes (MVLs), a project which we started developing in 2013. This new commercial process yields a bupivacaine MVL composition with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, by measuring a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25° C. Erucic acid is a degradation product of dierucoyl phosphatidyl choline (DEPC), one of the lipid components used to form MVL lipid membrane. Since DEPC has the highest concentration of all the lipid components, erucic acid was used as the marker to assess lipid stability of the bupivacaine MVLs. The bupivacaine MVLs manufactured by the claimed process ha[ve] a target concentration of bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL and can be directly administered to a patient without further purification. The product is expected to have a shelf life of up to 2 years when properly handled and stored at 5° C.

JTX-4001.2179.

36. In her declaration, Ms. Los referenced purportedly reduced degradation "over a period of six months at 25° C." In context, this statement implied to the Examiner that the 200-liter product had lower erucic acid concentration at the one-month timepoint in independent claim 1, as well as at the two-, three-, and six-month timepoints of the dependent claims. It would have made no procedural sense to submit an inventor declaration that was limited to discussion of only the six-month

timepoint, as most claims only incorporated the one-month limitation. *See* Tr. 647:13-648:7 (Slifer); JTX-4001.2179.

37. In the same paragraph as her discussion of purportedly "improved stability," Ms. Los told the USPTO that the claimed product had a "target concentration of bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL" and that it was "expected to have a shelf life of up to 2 years when properly handled and stored at 5°C." JTX-4001.2179. Ms. Los did not mention in her declaration that both of these properties were also true of prior art EXPAREL. Tr. 648:8-21 (Slifer); JTX-4001.2179.

38. In Paragraph 6 of Ms. Los's declaration to the USPTO, Ms. Los argued that the prior art did not teach the same two limitations that Dr. Dai had previously discussed with the Examiner—the "erucic acid level recited in [the] instant claims" (i.e., the one-month limitation, which was present in all of the claims and was the only erucic acid level recited in most of the claims) and the bupivacaine concentration of "from about 12.6 mg/mL to about 17.0 mg/mL." Tr. 648:22-649:23 (Slifer); JTX-4001.2180.

39. On May 7, 2021, the Examiner issued a Notice of Allowance after receiving Pacira's submissions. *Id.* at JTX-4001.2304. The Examiner stated the following Reasons for Allowance:

> The following is an examiner's statement of reasons for allowance: The declaration of Ms. Los attests that the

> method claims as amended are not obvious in view of the teachings of Camu in view of Li. The prior art fails to teach the claimed degradation product of erucic acid after 6 months storage at 25C. Furthermore the combined art does not teach the claimed concentration of bupivacaine. The Office finds the declaration persuasive that the combined prior art does not teach the claimed method of preparation of MVL having the claimed storage stability.

Id. at 4001.2311.

40. The Examiner stated that in view of the Los Declaration, he was persuaded that "the combined prior art does not teach the claimed method of preparation of MVL having the claimed storage stability" or "the claimed concentration of bupivacaine," and that his rejection was therefore withdrawn. *Id.* at 4001.2309. Paragraph 8 of the Reasons for Allowance identifies two limitations as the basis for allowance: the concentration of erucic acid, and the concentration of bupivacaine. Tr. 651:23-652:9 (Slifer); JTX-4001.2311. The Examiner explicitly relied on Ms. Los's declaration as a basis for his Reasons for Allowance. Tr. 652:10-14 (Slifer); Tr. 842:21-843:9 (Godici); JTX-4001.2311.

41. The Examiner's statement regarding "erucic acid after six months' storage at 25° C" referred to erucic acid at all timepoints over a six-month period (i.e., one, two, three, and six months), not just the six-month timepoint. Tr. 651:23-652:21 (Slifer). It would not make procedural sense for the Examiner's Reasons for Allowance to focus only on the six-month timepoint, because all of the claims had the one-month limitation (including claim 1, the only independent claim), and only

two of the 25 claims had the six-month limitation. *See* Tr. 652:15-653:2 (Slifer); JTX-4001.2311.

42. Dr. Dai filed "Comments on the Reasons for Allowance," stating that the Examiner's Reasons for Allowance might be inaccurate or incomplete, but did not provide any details as to potential problems with the Examiner's Reasons for Allowance. Tr. 653:9-654:7 (Slifer); JTX-4001.2355. Specifically, Dr. Dai's Comments stated that "the Statement of Reasons for Allowance, pursuant to MPEP 1302.14, is not intended to necessarily state all the reasons for allowance or all the details why claims are allowed" and that "the fact that Applicant has not specifically commented on the Examiner's characterizations of the reasons for allowance in the Statement of Reasons for Allowance shall not be taken as an acknowledgement of the accuracy of such characterizations." JTX-4001.2355.

43. Figure 3B was not discussed by the applicants or the Examiner during prosecution of the '495 Patent. *See* JTX-4001; Tr. 654:13-655:4 (Slifer); Tr. 850:6-9 (Godici).

44. Pacira did not disclose any data on the "current commercial process" (i.e., 45-liter EXPAREL) to the USPTO other than what appears on the face of the '495 Patent. Tr. 637:18-21 (Slifer); Tr. 859:19-861:4 (Godici).

3. Claims of the '495 Patent

45. The '495 Patent issued with 22 claims, all of which Pacira initially asserted against Defendants in this litigation. JTX-4121.20-21; D.I. 1. At trial, Pacira only asserted claim 7, which depends from claim 1. Those claims recite:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

7. The composition of claim 1, wherein the erucic acid concentration in the composition is about 99 μg/mL or less after the composition is stored at 25° C. for six months.

Id. at 4121.20-21(22:43-23:13, 23:28-31).

46. Claim 1 of the '495 Patent is the only independent claim, directed to a "composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial-scale process." *Id.* at 4121.20 (22:43-45); D.I. 187 at 16-17. Claim 1 also requires that "the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month." JTX-4121.20 (22:43-45).

47. Steps (a)-(f) of claim 1, and the requirement that all steps be "carried out under aseptic conditions," are "product-by-process" limitations. D.I. 187 at 17, n.11; PTO Tab 5 ¶ 14. These limitations are directed to the same process steps that Pacira has used to manufacture 45-liter commercial-scale batches of EXPAREL® since 2012. Tr. 105:23-106:6 (Hall); Tr. 182:21-185:25 (Grigsby). Batches of EXPAREL®, commercially available before January 22, 2021, practiced all limitations of claim 1. Tr. 442:10-16, 445:7-446:22 (Schwendeman).

48. Claim 7 is directed to "the composition of claim 1, wherein the erucic acid concentration in the composition is about 99 μg/mL or less after the composition is stored at 25° C. for six months." JTX-4121.20. Batches of EXPAREL®,

commercially available before January 22, 2021, practiced all limitations of claim 7. DTX-3110; Tr. 443:12-15 (Schwendeman).

49. Although claims 1, 3, and 5 are no longer asserted by Pacira, Defendants assert that Pacira committed inequitable conduct in seeking at least claims 1, 3, 5, and 7 before the USPTO.

50. Claim 3 is directed to "the composition of claim 1, wherein the erucic acid concentration in the composition is about 38 μg/mL or less after the composition is stored at 25° C. for two months." JTX-4121.20. Batches of EXPAREL®, commercially available before January 22, 2021, practiced all limitations of claim 3. Tr. 414:12-415:24, 425:18-426:8 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-3111.

51. Claim 5 is directed to "the composition of claim 1, wherein the erucic acid concentration in the composition is about 54 μg/mL or less after the composition is stored at 25° C. for three months." JTX-4121 at 20. Batches of EXPAREL®, commercially available before January 22, 2021, practiced all limitations of claim 5. Tr. 414:12-415:24, 425:18-426:7 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-3110.

52. Claim 8 is directed to "the composition of claim 7, wherein the composition has a pH of about 6.5 after the composition is stored at 25° C. for six months." Batches of EXPAREL®, commercially available before January 22, 2021,

practiced all limitations of claim 8. Tr. 414:12-415:24, 425:18-426:8 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-3110.

D. PERSON OF ORDINARY SKILL IN THE ART

53. A POSA, at the time of the effective filing date of the '495 Patent, would have been a person having a Ph.D., master's degree, and/or bachelor's degree in any of the pharmaceutical sciences, including chemistry, medicinal chemistry, chemical engineering, pharmaceutics, or a related field, with an understanding of the importance, use, and characterization of liposomal drugs in the pharmaceutical industry and several years of research experience in developing, formulating, characterizing, and/or analyzing pharmaceutical products, specifically controlled release drug products using drug delivery vehicles formed by emulsion or double emulsion processes, e.g., liposomes, or a person with equivalent knowledge from experience in the field. Tr. 384:2-17 (Schwendeman); Tr. 554:17-555:2 (Yaman). A POSA would also have had some experience in process engineering and scale-up of a liposomal product, or would have had access to consult with someone with such experience. Tr. 384:2-17 (Schwendeman); Tr. 554:17-555:2 (Yaman).

E. EXPAREL®

54. EXPAREL® was approved by the FDA in 2011, as a treatment for post-surgical analgesia. Tr. 80:5-8, 91:14-15 (Hall); DTX-3115; JTX-4205; PTO Tab 5 ¶ 19.

55. EXPAREL® was launched commercially in the United States in 2012. Tr. 91:16-18 (Hall); PTO Tab 5 ¶ 20.

56. EXPAREL® was in public use and on sale in the United States before January 22, 2021, and is therefore prior art to the '495 Patent. *See* Tr. 444:12-23 (Schwendeman); DTX-3109; PTO Tab 5 ¶ 20.

57. Since EXPAREL® was commercially launched in 2012, Pacira has sold close to 2,600 batches, amounting to about 10.5 million vials. DTX-3109; Tr. 443:12-23, 452:2-12 (Schwendeman).

58. The active ingredient in EXPAREL® is bupivacaine, which is also known as 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide. Tr. 74:21-24 (Hall); DTX-3115.23-24; JTX-4205.19; PTO Tab 5 ¶ 24. The inactive ingredients in EXPAREL® that form the multivesicular liposome include 4.7 mg/mL cholesterol, 0.9 mg/mL 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) ("DPPG"), 2.0 mg/mL tricaprylin, 8.2 mg/mL 1, 2-dierucoylphosphatidylcholine ("DEPC"). DTX-3115.23-24, JTX-4205.19. The median diameter of the liposome particles ranges from 24 to 31 μm, and the external pH of EXPAREL® is in the range of 5.8 to 7.4. DTX-3115.23-24, JTX-4205.19.

59. DEPC is the main lipid component in the EXPAREL MVLs. Tr. 152:22-23 (Grigsby); Tr. 486:8-10 (Schwendeman). The API bupivacaine is encapsulated inside the lipid membrane chambers in the presence of phosphoric acid

during the manufacturing process. Tr. 89:7-24 (Hall); Tr. 485:14-18 (Schwendeman).

60. In 2011, the FDA approved EXPAREL® for local administration to provide post-surgical analgesia. PTO Tab 5 ¶ 19; Tr. 91:14-15 (Hall). In 2018, the FDA approved EXPAREL® with a two-year shelf life as an interscalene brachial plexus nerve block to provide post-surgical regional analgesia, and in April 2018, EXPAREL®'s prescribing information was updated to reflect this new indication ("2018 EXPAREL® Label"). JTX-4205. The 2018 EXPAREL® Label is prior art to the '495 Patent as it was published at least on the FDA website before January 22, 2021. *Id.*

61. Prior to issuance of the '495 Patent, Pacira had listed the '838 Patent in the Orange Book for EXPAREL®. Tr. 338:25-340:1 (Molloy); DTX-2019. The '838 Patent expired on December 24, 2021. *Id.*

F. MANUFACTURING OF MVLS

1. Manufacturing MVLs using a Double Emulsion Process Was Known in the Prior Art

62. MVLs, including EXPAREL®, are manufactured via the creation of a water-in-oil-in-water ("w/o/w") double emulsion. Tr. 557:7-10 (Yaman); Tr. 108:9-12, 118:5-119:2 (Hall); JTX-4107.4-6. An aqueous solution is first mixed with a lipid-containing solution to create a water-in-oil ("w/o") emulsion. Tr. 89:7-24 (Hall); Tr. 557:13-20 (Yaman); JTX-4107.4-6. In this w/o emulsion, the lipids from

the lipid-containing solution form the outer liposome membrane layer, while the aqueous solution is contained inside. Tr. 557:24-558:1 (Yaman). During this first emulsion step, if the API is bupivacaine and is included in the lipid phase, as with EXPAREL®, the bupivacaine is encapsulated within the lipid membrane. Tr. 557:24-558:1 (Yaman).

63. The w/o emulsion is next mixed with a second aqueous solution, to create the w/o/w second emulsion. Tr. 108:9-12 (Hall); Tr. 559:2-7 (Yaman); JTX-4107.4-6. For EXPAREL®, this aqueous solution includes dextrose and lysine. Tr. 90:14-20, 108:9-12 (Hall); JTX-4107.4-6. In this w/o/w emulsion, the unilamellar "bubble" liposomes form together to create the multivesicular "pomegranate" liposomes. Tr. 89:25-90:8 (Hall); 559:7-10 (Yaman).

64. In general, the MVLs formed via the second emulsion are then stirred in the presence of nitrogen gas (i.e., "sparged") to evaporate the organic solvent, and in the process the liposomes harden. Tr. 90:21-91:4 (Hall); Tr. 560:18-561:6 (Yaman); JTX-4107.4-6. Then the MVLs are concentrated and washed several times with saline. Tr. 91:5-13 (Hall); 561:7-20 (Yaman); JTX-4107.4-6. During this manufacturing process, dextrose and lysine are used as processing aids in order to assist in the formation of MVLs. Tr. 91:6-10 (Hall); 165:5-8 (Grigsby). Finally, the MVL solution is concentrated to reach a target drug concentration. Tr. 91:11-13 (Hall); JTX-4107.4-6. For EXPAREL®, the target concentration is 13.3 mg/mL.

Tr. 185:6-9 (Grigsby); DTX-3115. This method of manufacturing MVLs is sometimes known as the DepoFoam method, and has been known in the art since at least 2002. Tr. 563:25-564:6 (Yaman); JTX-4202.

2. Manufacturing Process for EXPAREL®

65. Pacira currently manufactures EXPAREL® at two different commercial scales: a 45-liter commercial scale process, and a 200-liter commercial scale process. Tr. 454:6-14 (Schwendeman); Tr. 96:16-18 (Hall); Tr. 771:9-19 (Klibanov). The two processes use the same basic manufacturing steps and the same materials (Tr. 118:5-22 (Hall); Tr. 167:7-12, 183:2-185:24 (Grigsby)), and produce comparable, equivalent product (Tr. 103:8-14 (Hall); Tr. 176:12-17, 177:12-14 (Grigsby); Tr. 441:21-443:1 (Schwendeman); JTX-4053.2; 4053.4; 4053.6; JTX-4187.4).

66. Pacira has never represented to FDA or to the public (aside from the papers it has filed with the Court for this litigation) that its 45-liter batches of EXPAREL® and its 200-liter batches of EXPAREL® have different properties. Tr. 176:12-178:5 (Grisby); Tr. 504:21-504:25 (Schwendeman); JTX-4053.2; 4053.4; 4053.6; JTX-4187.4. The EXPAREL® product is sold under the same label regardless of which manufacturing scale was used, because the product produced by each process is interchangeable—it has the same efficacy, safety, and characteristics. Tr. 117:1-15 (Hall); JTX-4502. Pacira does not inform patients or prescribers (and

patients and prescribers would not otherwise have a way to know based on publicly available information) which scale was used to manufacture any particular batch of EXPAREL®. Tr. 454:9-14 (Schwendeman).

67. According to Pacira's submissions to FDA, the process flow is maintained between the scales, as are the major processing steps, in order to produce EXPAREL® that is equivalent to the 45-liter scale product. Tr. 102:19-103:7 (Hall); JTX-4159; JTX-4174; JTX 4187; JTX 4188. Pacira's development of the 200-liter process aimed to match key 45-liter in-process and final product attributes, resulting in an equivalent product. Tr. 102:19-103:7 (Hall); Tr. 174:12-17 (Grigsby); JTX-4053.2; 4053.4; 4053.6.

68. Pacira's 45-liter and 200-liter manufacturing processes both start with the step of mixing a lipid solution containing the lipids DEPC, DPPG, cholesterol, and tricaprylin and the API bupivacaine, dissolved in methylene chloride solution, with an aqueous phosphoric acid solution. Tr. 118:5-23 (Grigsby). These two solutions are mixed by "high-shear" mixing to create a water-in-oil emulsion, which consists of aqueous droplets containing bupivacaine phosphate that are dispersed in the organic phase containing the lipid components. *Id.*; JTX-4148.9-12, .16, .19-20; JTX-4188.7-8.

69. Next, the water-in-oil emulsion is mixed with a dextrose/lysine solution at a "lower shear," to produce a water-in-oil-in-water emulsion, which consists of

spherules of methylene chloride/lipid solution that can contain aqueous droplets containing bupivacaine phosphate. Tr. 118:5-23 (Grigsby); JTX-4148.9-12, .20-22; JTX-4188.7-8.

70. Next, the water-in-oil-in-water emulsion is diluted, and the methylene chloride is removed by sparging the emulsion with nitrogen. Tr. 118:5-23 (Grigsby); JTX-4148.9-13; JTX-4188.6-7, .17-19. At the end of the sparge step, the emulsion is a suspension of MVL particles with encapsulated bupivacaine. Tr. 90:21-91:4 (Hall); 560:18-561:6 (Yaman); JTX-4148.9-12, .16; JTX-4188.19-20.

71. Next, the suspension is concentrated by a series of filtration steps, using tangential microfiltration to remove residual methylene chloride, dextrose, lysine, free bupivacaine, and phosphate. Tr. 118:5-23 (Hall); JTX-4148.9-12, .16, .32-33; JTX-4188.19-20. The filtration process consists of three operations: microfiltration to reduce the volume and concentrate the product, diafiltration to replace the dextrose/lysine solution with saline solution, and another round of microfiltration to concentrate the product to the target bupivacaine concentration of about 13.3 mg/mL. Tr. 118:5-23 (Hall); JTX-4148.9; JTX-4188.19-20.

72. All of these steps are performed under aseptic conditions. Tr. 119:3-9 (Hall); JTX-4148.12; JTX-4188.5.

73. For the scale-up to its 200-liter process, Pacira used the same manufacturing steps and materials as was used with the 45-liter commercial scale

process. Tr. 118:5-119:9 (Hall (agreeing that "[t]he 45-liter process uses all of those steps, A through F")); Tr. 183:2-185:25 (Grigsby (agreeing that limitations (a)-(f) of claim 1 "is the same between the 45-liter and 200-liter process)); Tr. 445:15-446:2 (Schwendeman (agreeing that "the prior art EXPAREL" was manufactured via "that same A through F double-emulsion process")), 447:3-6; Tr. 556:14-561:4 (Yaman); JTX-4148; JTX 4188.

74. With respect to the first emulsion step, the "[m]ixing parameters, including mixing speed, mixing time, blade height, blade diameter, and mixing temperature were evaluated to understand the impact on droplet size distribution, lipid incorporation, and emulsion conductivity." JTX-4148.16. With respect to the second emulsion step, "[m]ixing parameters, including mixing speed, mixing time, blade height, blade diameter, and mixing temperature were evaluated to understand the impact on particle size distribution, in-vitro release, and emulsion conductivity." *Id*. With respect to the solvent removal step, "[s]parge parameters, including nitrogen flow rate and distribution, mixing speed, and sparge temperature were evaluated to understand the impact on methylene chloride removal, sparge conductivity, and product yield." *Id*.; *see also* Tr. 571:24-572:10, 574:16-579:13, 580:20-24, 581:14-581:24, 583:24-584:24 (Yaman); JTX-4121.

75. With respect to the diafiltration step, "[d]iafiltration parameters, including retentate and permeate flow rates, nitrogen flush flow rate, and number of

volume exchanges were evaluated to understand the impact on processing time, methylene chloride removal, pH, and product yield." JTX-4148.16. After manufacturing batches to obtain data for submission to the FDA, "additional development was performed to reduce final product pH and residual methylene chloride such that they were both sufficiently below the final product upper specification limits." *Id.*

76. Pacira's first five batches that were manufactured at 200-liter scale were "aborted due to bupivacaine precipitation resulting in irreversible TFF fouling during buffer exchange." JTX-4148.25. According to Pacira, the bupivacaine precipitation (crystallization) was due to "heterogenous methylene chloride removal during the sparge step, leading to bupivacaine release and subsequent precipitation." *Id.* at 4148.42. In order to address the problem, Pacira designed different "sparge rings," which are tubular rings with holes to distribute the gas flow, placed in the interior of the tank. *Id.*

77. Pacira investigated a number of different process parameters when developing the 200-liter process. JTX-4188.7, 4188.9, 4188.10. Much of this experimentation was not disclosed in the '495 Patent. Tr. 807:12-811:16 (Klibanov).

78. Pacira evaluated different geometries, including placement of holes, before deciding on a design that reduced fouling during the filtration steps. JTX-4148.27.

79. Pacira manufactured three 200-liter registration batches (129855, 129856, 129860) and conducted accelerated stability testing on these batches. Tr. 134:21-24, 136:6-137:11 (Hall); 421:8-18, 437:20-437:25 (Schwendeman); DTX-2535. The results of this testing were submitted to the FDA and reported in the '495 Patent specification. JTX-4121.

80. Pacira's current 200-liter commercial process is not the same as the process it used to manufacture its three registration batches submitted to the FDA (and reported in the '495 Patent specification). Tr. 134:12-136:5 (Hall); JTX-4188.11. Pacira used 450 rpm for the mixing speed for the second emulsion step for its three registration batches; however it subsequently adjusted the speed to 495 rpm because the d_{90} particle size resulted in two of the three registration batches being outside the acceptable criteria. Tr. 134:12-136:5 (Hall); 438:7-440:8 (Schwendeman); JTX-4188.11

G. STORAGE, STABILITY, AND SHELF LIFE OF EXPAREL®

1. Storage, Shelf Life, and Stability Specifications for EXPAREL®

81. From 2012 through the present day, EXPAREL®'s recommended storage temperature has been 5±3 °C (i.e., refrigerated temperature). Tr. 154:20-22 (Grigsby); JTX-4205; DTX-3115.

82. As of EXPAREL®'s initial approval in October 2011, its shelf life was twenty-four (24) months at refrigerated temperature. Tr. 154:20-22 (Grigsby); JTX-4205; DTX-3115.

83. As of the present day, every batch of EXPAREL® has a shelf life of twenty-four (24) months at refrigerated temperature, regardless of whether it was manufactured using Pacira's 45- or 200-liter commercial-scale process. Tr. at 86:15-23 (Hall).

84. Pacira presented no evidence that it plans to change the shelf life of EXPAREL®.

85. FDA requires that all drug products undergo stability testing to ensure an accurate expiration date. JTX-4044; JTX-4045; DTX-3061.5. Some drug products should be stored at room temperature, some in a refrigerator, and some frozen, depending on stability characteristics. *See* JTX-4044.13-15. In order to establish the shelf life of drug products, stability can be examined at the recommended storage temperature, and also at higher temperatures as part of "accelerated" stability studies. *Id.*; JTX-4045.7. FDA requires that the shelf life of a drug product ultimately be demonstrated through real-time stability studies at the recommended storage temperature. JTX-4045.7; DTX-3061.12.

86. Even if the FDA accepted accelerated stability studies (i.e., stability studies conducted at 25° C, which is higher than the recommended storage

temperature for EXPAREL®) to grant a longer shelf life, and even if the six-month time point from accelerated stability testing of EXPAREL® predicted its stability during normal storage, the results from Pacira's stability testing of the three 200-liter batches reported in the '495 Patent would have led to a ***shorter*** shelf life. These three 200-liter batches had a d_{90} greater than 62.0 µm at six months of storage at 25° C, and, thus, were outside the acceptable stability criteria for refrigerated storage during the 24-month shelf life. Tr. 134:12-136:5 (Hall); Tr. 437:8-440:8 (Schwendeman); JTX-4188.11.

87. There is no marketing "competitive advantage" when an alleged difference in formulation stability does not result in a longer shelf life, as is the case with 200-liter batches of EXPAREL®. *See, e.g.*, Tr. 454:6-14 (Schwendeman); JTX-4205; DTX-3115.

88. Pacira's stability specification for erucic acid in EXPAREL® (manufactured by either process) is no more than 310 µg/mL erucic acid after storage at 5° C for 24 months. Tr. 157:23-158:1, 205:10-15 (Grigsby); JTX-4159.42; JTX-4264.5.

89. EXPAREL® has no stability specification for storage at 25° C. Tr. 195:23-196:15, 204:20-206:3 (Grigsby).

90. Pacira's Quality Control ("QC") department (responsible for stability testing) and Pacira's regulatory group are unaware of any differences in stability

properties between 45-liter and 200-liter EXPAREL. JTX-4290.5-6 (Glenn Tr. 204:06-209:13). Pacira has represented to the FDA that the stability of its 200-liter batches is equivalent to that of its 45-liter batches, with similar trends and values within historical ranges; it has never represented to the FDA that there are any differences in stability between batches made with the 200-liter process and those made with the 45-liter process. Tr. 176:12-178:5 (Grigsby); 504:21-25 (Schwendeman); JTX-4053.2, .4, .6; JTX-4187.4.

2. Stability Data for 45-Liter Batches of EXPAREL®

91. Between 2012 and January 22, 2021, Pacira periodically tested batches of EXPAREL® for stability. *See, e.g.*, DTX-3110. Various properties of EXPAREL® were tested during stability testing, including total bupivacaine levels, percent free bupivacaine, percent packed particle volume, particle size (d_{10}, d_{50}, and d_{90}), *in vitro* release (IVRA), pH, erucic acid concentration, particulate matter, and sterility. *See, e.g.*, DTX-2465; PTX-108; PTX-228.

92. Some batches were tested for stability at 25° C. Tr. 154:9-15 (Grigsby).

93. Pacira's QC department performed stability testing and maintained records of the results for each batch. JTX-4290.3-5 (Glenn Tr. 49:11-49:16, 53:24-54:05); Tr. 204:06-13 (Grigsby). The QC department provided this data to other groups at Pacira upon request. *See, e.g.*, DTX-2465.

94. Prior to January 22, 2021, Pacira tested a very limited number of batches of EXPAREL® manufactured using Pacira's 45-liter commercial process for stability after six months storage at 25° C. Of the nearly 2,600 commercial batches made and sold, Pacira tested only eight (8) at these conditions. Tr. 452:2-12, 524:6-17 (Schwendeman); DTX-3109; DTX-3111. Pacira tested approximately forty (40) additional batches under these conditions, which were used, for example, to support regulatory filings or bioequivalence studies. Tr. 419:10-20 (Schwendeman); DTX-3109; DTX-3110. This accelerated stability testing was performed according to approved stability protocols, and Pacira submitted the stability data to the FDA in support of Pacira's New Drug Application ("NDA") for EXPAREL®. DTX-2465; JTX-4241.

95. Batches 14-4012, 14-4013, 14-4015, 16-3089, 16-3088, 16-3090, 18-P004 and 18-P063 were all tested for stability at 25° C. DTX-3110. Each of these batches was commercially sold, with the first sale dates on March 3, 2015; March 12, 2015; April 29, 2015; September 27, 2016; October 19, 2017; November 18, 2018; and April 25, 2019 (3-11-2015, 3-12-2015, 4-29-2015, 9-27-2016, 9-27-2016, 10-19-2017, 11-18-2018, and 4-25-2019), respectively. DTX-3109.

96. The batches that were measured at 25° C for stability but not sold commercially were "registration batches" or "PPQ batches." DTX-2465. The physical properties of Pacira's "registration batches" of EXPAREL® and "PPQ

batches" of EXPAREL® were representative of the physical properties of Pacira's commercial lots of EXPAREL®, including their stability properties when stored at 25° C for up to six months. Tr. 190:8-20 (Grigsby); Tr. 451:3-22 (Schwendeman). Each of these "registration batches" and "PPQ batches" was manufactured using the same process, components, and equipment as Pacira's commercial batches, during the same time period. Tr. 187:15-20 (Grigsby). Pacira has not identified any systematic differences in stability properties between its registration and PPQ batches or its commercial batches, or any difference in manufacturing that would be expected to give rise to differences in stability properties.

97. Prior to January 22, 2021, some 45-liter batches of EXPAREL® that Pacira tested for stability had the claimed ranges of erucic acid and external pH after storage for one, two, three, and/or six months at 25 °C. DTX-3110. Other 45-liter batches of EXPAREL® did not. *Id.*

3. Stability Data for 200-Liter Batches of EXPAREL®

98. As with the 45-liter batches of EXPAREL® tested for stability at 25° C, some 200-liter batches tested for stability at 25° C have fallen within the claimed ranges of erucic acid. DTX-3114. Other batches have not. *Id.*

99. During development of the 200-liter process, Pacira manufactured the three 200-liter registration batches listed in the specification of the '495 Patent. Tr. 136:6-137:11 (Hall); Tr. 421:8-18, 437:20-437:25 (Schwendeman); DTX-2535.

However, these registration batches fell outside expected stability results for a different parameter, d_{90} particle size during accelerated testing; as of January 2021, they were expected to fail to meet stability criteria for d_{90} particle size during refrigerated storage. Tr. 134:12-136:5 (Hall); 438:7-440:8 (Schwendeman); JTX-4188.11.

100. In an attempt to address this problem, Pacira changed one of the manufacturing parameters for its 200-liter process (the so-called "new" process referred to in the '495 Patent)—specifically, the mixing speed for the second emulsion. Tr. 134:12-136:5 (Hall); 438:7-440:8 (Schwendeman); JTX-4188.11.

101. Using the new parameters, Pacira manufactured three additional regulatory batches and three batches that were sold commercially, and conducted accelerated stability testing on all six batches: 120862, 120863, 120864, 21-2001, 21-2002, and 21-2003. Tr. 134:12-136:5 (Hall); 438:7-440:8 (Schwendeman); JTX-4188.11.

102. At least three of the six batches manufactured with the 495 rpm mixing speed were commercially sold: 21-2001, 21-2002, and 21-2003. DTX-3113; DTX-3109. None of these three commercially-sold batches had an erucic acid concentration of "about 23 µg/mL or less" after one month at 25° C (Tr. 440:9-441:19 (Schwendeman); DTX-3113), nor did any of these batches have an erucic acid concentration of "about 99 µg/mL or less" after six months at 25° C. Tr. 461:13-

22 (Schwendeman); Tr. 139:20-141:11, 142:16-143:8, 143:14-144:2 (Hall); DTX-3113; DTX-2551; DTX-2552; DTX-2553. Thus, none of the commercially-sold 200 liter batches manufactured with the 495 rpm mixing speed met the limitations of claim 7 of the '495 Patent.

103. Of the 200 liter batches 120862, 120863, and 120864, two out of the three had a erucic acid concentration greater than "about 23 µg/mL or less" after one month and greater than "about 99 µg/mL or less" after six months.[1] Tr. 437:20-441:19 (Schwendeman); DTX-3114.

104. Thus, out of the nine batches of 200-liter product that Pacira made and tested under accelerated storage conditions, two failed the d_{90} stability requirements, and five failed to meet the erucic acid concentration limitations of claim 7 of the '495 Patent. *Id*. Only two of the nine met both the FDA d_{90} specifications, and the erucic acid limitations of claim 7 of the '495 Patent. *Id.*

105. None of the commercial 200-liter batches which Pacira has tested for stability at 25° C have fallen within the erucic acid ranges claimed in the '495 Patent. Tr. 439:10-440:20, 460:14-23 (Schwendeman); DTX-3113.

[1] Pacira sometimes refers to batches of EXPAREL® as "lots," and sometimes as "batches." The two terms are interchangeable, at least for EXPAREL®.

II. INVALIDITY

A. ANTICIPATION

1. Claim 1 Is Anticipated by the Prior Art EXPAREL® Product

106. Batches of EXPAREL® that were commercially available, on sale, or publicly available before January 22, 2021 ("the Prior Art EXPAREL® Product") practiced each limitation of claim 1 of the '495 Patent. Tr. 444:8-446:23 (Schwendeman). Claim 1 is anticipated by one or more batches of the Prior Art EXPAREL® Product that were commercially available, on sale, or publicly available before January 22, 2021. Tr. 443:9-15, 445:7-447:22 (Schwendeman).

a. "A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising"

107. The preamble of claim 1 recites "a composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising." JTX-4121.20 (22:43-45).

108. "The Prior Art EXPAREL® Product is a suspension of aqueous multi vesicular liposomal (MVL) particles containing encapsulated bupivacaine." DTX-2498.21; *see also* Tr. 119:23-120:9 (Hall); Tr. 183:2-185:25 (Grigsby); Tr. 443:20-24, 444:8-3 (Schwendeman); JTX-4205; DTX-3115. The FDA-approved label (e.g., the 2018 EXPAREL Label) for the Prior Art EXPAREL® Product describe the

product as an "aqueous suspension of multivesicular liposomes . . . containing bupivacaine" where the liposomes are "encapsulat[ed]." JTX-4205.

109. The Prior Art EXPAREL® Product was a commercial product that was manufactured using a 45-liter commercial scale process. Tr. 94:10-12, 118:5-119:9 (Hall); 183:7-9 (Grigsby); *see also* Tr. 445:7-446:2 (Schwendeman); Tr. 561:21-562:2 (Yaman); DTX-2498.3 (describing the Prior Art EXPAREL® Product as being manufactured "at commercial scale").

b. Process steps (a)-(f) of claim 1

110. Limitations (a)-(f) of claim 1 describe the process by which the claimed invention must be made. The parties agree that limitations (a)-(f) are product-by-process limitations. PTO Tab 5 ¶ 14. Because these steps are product-by-process limitations, they are not deemed limiting for purposes of evaluating anticipation and obviousness. *See* COL ¶ 28. Even if these process steps were limiting, they were met by the Prior Art EXPAREL® Product. According to the named inventors, Pacira made the Prior Art EXPAREL® Product according to the steps described in limitations (a)-(f) of claim 1. Tr. 118:5-119:9 (Hall (agreeing that "[t]he 45-liter process uses all of those steps, A through F")); Tr. 183:2-185:25 (Grigsby (agreeing that limitations (a)-(f) of claim 1 "is the same between the 45-liter and 200-liter process)); Tr. 445:15-446:2 ((agreeing that "the prior art EXPAREL" was manufactured via "that same A through F double-emulsion process"), 447:3-6

(Schwendeman); Tr. 556:14-561:4 (Yaman); JTX-4174; JTX-4159; JTX-4174; JTX 4187; JTX 4188.

111. The Prior Art EXPAREL® sold or offered for sale before January 22, 2021 was prepared by a process comprising:

- mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine ("DEPC"), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) ("DPPG"), and at least one neutral lipid. Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 423:13-20, 446:4-7 (Schwendeman)

- mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose. Tr. 118:5-119:9 (Hall); 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 424:12-18, 447:3-6 (Schwendeman).

- removing the volatile water immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume. Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 424:12-19, 447:3-6 (Schwendeman).

- reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume. Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 424:12-19, 447:3-6 (Schwendeman).

- exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume. Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 424:12-19, 447:3-6 (Schwendeman).

- further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to

about 17.0 mg/mL. Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); *see also* JTX-4174; Tr. 424:12-425:7, 447:3-6 (Schwendeman).

112. Pacira manufactured batches of Prior Art EXPAREL® at two different sites, i.e., San Diego, California (USA) and Swindon, UK. Tr. 349:21-350:3 (Molloy). All batches were made according to the manufacturing process for EXPAREL® that Pacira submitted to the FDA. *See* Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby).

c. "wherein all steps are carried out under aseptic conditions"

113. Claim 1 also recites "wherein all steps are carried out under aseptic conditions." JTX-4121.20 (22:43-23:12). The parties agree that this clause is a product-by-process limitation. D.I. 187 at 17. Because this step is a product-by-process limitation, it is not deemed limiting for purposes of evaluating anticipation and obviousness. *See* COL ¶28. Even if this clause were limiting, it was met by the Prior Art EXPAREL® Product. The process used to prepare the Prior Art EXPAREL® Product was carried out under aseptic conditions. Tr. 119:3-9 (Hall (agreeing that "[t]he 45 liter process was performed under aseptic conditions")); Tr. 185:10-16 (Grigsby); *see also* Tr. 424:12-21 (Schwendeman (discussing commercially sold batches of Prior Art EXPAREL described in DTX-3111)).

d. "wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month"

114. According to Pacira, it produced sales records for all batches of Prior Art EXPAREL® Product that were commercially sold prior to January 22, 2021 in response to discovery requests served in the litigation. DTX-3109 (summary of Pacira sales records). As part of the accelerated stability studies on the Prior Art EXPAREL® Product, Pacira stored forty-eight batches of the Prior Art EXPAREL® Product at 25° C for six months and tested those batches for erucic acid concentrations. *See, e.g.*, DTX-3110; DTX-3111; DTX-2465; DTX-2482; DTX-2498; PTX-108.

115. Pacira's expert agrees that at least one commercially sold batch of Prior Art EXPAREL® Product had an erucic acid concentration in the final aqueous suspension of bupivacaine encapsulated MVLs of "about 23 µg/mL or less after the composition was stored at 25° C for one month." Tr. 763:9-25 (Klibanov); *see also* Tr. 425:1-17, 447:12-448:9 (Schwendeman); DTX-3110.

116. As part of the accelerated stability studies on the Prior Art EXPAREL® Product, Pacira stored ten batches of commercially-sold Prior Art EXPAREL® Product at 25° C. *See, e.g.*, DTX-3111; DTX-2465.44, .50, .52; DTX-2482; DTX-2498; PTX-108. At least six of these ten commercially-sold batches of the Prior Art EXPAREL® Product had an erucic acid concentration of less than about 23 µg/ml

after storage at 25° C for one month. DTX-3111; Tr. 448:2-15 (Schwendeman); Tr. 763:9-25 (Klibanov).

117. Because every limitation of claim 1 of the '495 Patent was practiced by the Prior Art EXPAREL® Product, claim 1 is invalid as anticipated by the Prior Art EXPAREL® Product. DTX-3111; Tr. 449:1-14 (Schwendeman); Tr. 764:9-25 (Klibanov).

e. Unclaimed "Structural and Functional Features"

118. At trial, Plaintiffs' expert Dr. Klibanov offered his own interpretation of the Court's claim construction decision with respect to the term "prepared by a commercial scale process," which he interpreted to require (1) a process practiced on a scale larger than 45 liters, and (2) "new structural features" including "lower lipid hydrolysis, higher internal lysine and dextrose concentrations, more desirable internal pH . . . and finally, improved MVL particle strength during product transportation." Tr. 700:16-701:16, 703:25-704:12, 752:7-753:2 (Klibanov).

119. The evidence at trial further supported the Court's claim construction opinion that no specific volume range is implied by "prepared by a commercial scale process." ECF 187 (Claim Construction Opinion) at 20 n.12; *see id.* at 31 (construing "commercial scale" as "a scale of manufacturing for production of a commercial product"). The named inventors on the '495 Patent consistently testified to their understanding that Pacira's 45-liter manufacturing process for prior art

EXPAREL® was a "commercial scale" process. Tr. 94:7-12 (Hall); Tr. 183:7-9 (Grigsby); JTX-4289.10 (Los Tr. 61:3-5, 61:7-11, 61:14).

120. Other than the MVLs "having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL" bupivacaine, and having an erucic acid concentration of less than about 23 µg/mL after six months of storage at 25° C, claim 1 recites no additional "structural an functional" features. JTX-4121.20-21.

121. Consistent with the language of the claim, the named inventors on the '495 Patent testified that to their understanding, the only specified physical properties in claim 1 were the one-month erucic acid limitation and the concentration of bupivacaine. JTX-4289.15 (Los Tr. 79:13-14, 79:20-80:5, 80:9-11); Tr. 183:2-185:25 (Grigsby); JTX-4287.6 (Ardekani Tr. 78:1-19, 80:13-16, 80:18).

122. As described above, the Prior Art EXPAREL Product had the claimed bupivacaine concentrations and erucic acid concentrations. *Supra* ¶ 115.

123. To the extent the claimed steps (a)-(f) affect the structure or function of the product made by that product, a person of ordinary skill in the art would have understood the Prior Art EXPAREL® Product also possessed those structure(s) and/or feature(s) as claimed because those claimed steps were used in the manufacture of that prior art product. *See* Tr. 183:2-185:25 (Grigsby); Tr. 447:3-6, 510:17-21 (Schwendeman); Tr. 852:2-21 (Godici); JTX-4174. Dr. Klibanov admits that any of the "structures and functions" he believes to be "new" in the 200-liter

process would "stem from . .. the process parameters" that "aren't in the claim limitations." Tr. 806:15-25 (Klibanov).

124. The Prior Art EXPAREL is prepared "at commercial scale," and EXPAREL manufactured at either 45-liter scale or 200-liter scale will have the same structural and functional features. Tr. 509:12-22, 460:9-15 (Schwendeman). Pacira put forth no evidence of any "structural and functional features" that differ between the Prior Art EXPAREL and the claimed composition to rebut Defendants' position; nor does Pacira have any such evidence. *See, e.g.*, Tr. 786:2-9 (Klibanov) (Pacira's expert admitted that he "didn't do any investigation of whether there were improved structural or functional features when [he] compared batches made at 45 liters with batches made at 200 liters.").

2. Claim 3 Is Anticipated by the Prior Art EXPAREL® Product

125. Claim 3 depends from claim 1, and adds that the erucic acid concentration in the composition is "about 38 μg/mL or less after the composition was stored at 25° C for two months." JTX-4121.21. Although Pacira did not assert claim 3 at trial, anticipation of claim 3 is nonetheless relevant to Pacira's inequitable conduct.

126. At least one commercially sold batch of Prior Art EXPAREL® Product had an erucic acid concentration in the final aqueous suspension of bupivacaine encapsulated MVLs of "about 38 μg/mL or less after the composition was stored at

25° C for two months." Tr. 764:9-25 (Klibanov); *see also* Tr. 414:12-24, 425:18-426:8 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-2465.44, .50, .52; DTX-3111.

127. As part of the accelerated stability studies on the Prior Art EXPAREL® Product, Pacira stored ten batches of commercially-sold Prior Art EXPAREL® Product at 25° C. *See, e.g.*, DTX-3111; DTX-2465; DTX-2482; DTX-2498; PTX-108. At least six of these ten batches were found to have an erucic acid concentration of less than about 38 µg/ml after storage at 25° C for two months. Tr. 414:12-415:25, 425:18-426:8 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-2465.44, .50, .52, DTX-3111. Specifically, commercially-sold batches 14-4012, 14-4013, 14-4015, 16-3088, 16-3089, and 16-3090 had an erucic acid concentration of less than about 38 µg/ml after storage at 25° C for two months. JTX-4079.2; JTX-4037.18; DTX-2465.44, .50, .52; DTX-3111; Tr. 764:12-23 (Klibanov).

128. Of the six commercially sold batches 14-4012, 14-4013, 14-4015, 16-3088, 16-3089, and 16-3090 that had an erucic acid concentration of less than about 38 µg/ml after storage at 25° C for two months, five also had an erucic acid concentration of less than about 23 µg/ml after storage at 25° C for one month (batch numbers 14-4013, 14-4015, 16-3088, 16-3089, and 16-3090). JTX-4079.2; JTX-4037.18; DTX-2465.44, .50, .52; DTX-3111; Tr. 414:12-415:24, 425:18-426:8 (Schwendeman); Tr. 764:12-23 (Klibanov).

129. Thus, commercially sold batches 14-4013, 14-4015, 16-3088, 16-3089, and 16-3090 met both the claim 1 and claim 3 erucic acid concentration limitations, and anticipate claim 3.

3. Claim 5 Is Anticipated by the Prior Art EXPAREL® Product

130. Claim 5 depends from claim 1, and adds that the erucic acid concentration in the composition is "about 54 μg/mL or less after the composition is stored at 25° C for three months." JTX-4121. Although Pacira did not assert claim 5 at trial, anticipation of claim 5 is nonetheless relevant to Pacira's inequitable conduct.

131. Pacira's expert agrees that at least one commercially sold batch of Prior Art EXPAREL® Product had an erucic acid concentration in the final aqueous suspension of bupivacaine encapsulated MVLs of "about 54 μg/mL or less after the composition was stored at 25° C for three months." Tr. 764:9-25 (Klibanov); *see also* Tr. 414:12-415:25, 424:19-425:9 (Schwendeman); JTX-4037.18; JTX-4079.2; DTX-2465.44, .50, .52; DTX-3110.

132. As part of the accelerated stability studies on the Prior Art EXPAREL® Product, Pacira stored ten batches of commercially sold Prior Art EXPAREL® Product at 25° C. *See, e.g.*, DTX-3111; DTX-2465.44, .50, .52; DTX-2482; DTX-2498; PTX-108. At least four of these ten batches were found to have an erucic acid concentration of less than about 54 μg/ml after storage at 25° C for three months.

Tr. 414:12-415:25, 425:18-426:8(Schwendeman); JTX-4037.18; JTX-4079.2; DTX-2465.44, .50, .52; DTX-3111. Specifically, commercially sold batches 14-P004, 16-3088, 16-3089, and 16-3090 had an erucic acid concentration of less than about 54 µg/ml after storage at 25° C for three months. JTX-4079.2; JTX-4037.18; DTX-2465.44, .50, .52; DTX-3111; Tr. 414:12-415:25, 425:18-426:8 (Schwendeman); Tr. 764:12-23 (Klibanov).

133. Of the four commercially sold batches 14-P004, 16-3088, 16-3089, and 16-3090 that had an erucic acid concentration of less than about 54 µg/ml after storage at 25° C for three months, all four also had an erucic acid concentration of less than about 23 µg/ml after storage at 25° C for one month. JTX-4079.2; JTX-4037.18; DTX-2465.44, .50, .52; DTX-3111; Tr. 414:12-415:25, 425:18-426:8 (Schwendeman); Tr. 764:12-23 (Klibanov).

134. Thus, commercially sold batches 14-P004, 16-3088, 16-3089, and 16-3090 met both the claim 1 and claim 5 erucic acid concentration limitations, and anticipate claim 5.

4. Claim 7 Is Anticipated by the Prior Art EXPAREL® Product

135. Claim 7 depends from claim 1, and adds that the erucic acid concentration in the composition is "about 99 µg/mL or less after the composition is stored at 25° C for six months." JTX-4121; Tr. 391:18-392:1 (Schwendeman).

136. Numerous batches of the Prior Art EXPAREL® Product tested by Pacira provide evidence of the existence of commercially-available prior art batches that anticipate claim 7. DTX-3110; DTX-3111; Tr. 449:20-452:12 (Schwendeman). These 45-liter batches were "ready for patenting" before January 22, 2021 because they met each limitation of claim 7, and because EXPAREL had been shown to work for its intended purpose, at least because EXPAREL had been approved by the FDA. *See, e.g.*, *id.*; Tr. 91:16-21 (Hall); JTX-4205.

137. Pacira conducted accelerated stability testing on fifty-three batches of Prior Art EXPAREL® Product, forty-eight of which were tested after six months storage at 25° C. Tr. 447:7-22 (Schwendeman); DTX-3110. Pacira's expert agrees that the results from that testing shows that the manufacturing process for the 45-liter EXPAREL® creates a product with a range of erucic acid concentration after storage at 25° C. Tr. 708:7-15 (Klibanov); *see also* Tr. 447:23-448:2 (Schwendeman); DTX-3110.

138. As the FDA has instructed, "the manufacturing process used for" batches of drug product placed on formal stability studies "should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing." JTX-4044.11; *see also* Tr. 451:3-13 (Schwendeman).

139. Some of the fifty-three batches of Prior Art EXPAREL® Product were registration and PPQ batches, upon which Pacira relied for FDA approval of EXPAREL®; these batches also had an erucic acid concentration in the final aqueous suspension of bupivacaine encapsulated MVLs of about 23 μg/mL or less after the composition was stored at 25° C for one month. Tr. 447:12-448:9 (Schwendeman); DTX-3110.

140. Registration batches are manufactured according to the same process as commercial lots, and are "representative of the commercial lots." Tr. 392:5-12, 441:21-442:2, 522:10-15, 527:24-528:1 (Schwendeman). Registration batches that are made to qualify the product manufacturing process are used in a regulatory submission to get approval for the product. DTX-2465.3 (NDA excerpt attached to email chain, describing "registration" batches as those used "to support EXPAREL, 13.3 mg/mL Manufactured at Patheon"); Tr. 393:4-11 (Schwendeman); Tr. 136:6-137:10 (Hall (agreeing that stability data on 200 liter registration batches were submitted to the FDA as part of the approval for Pacira's 200 liter process). Process performance, or "PPQ" batches, are used with registration batches as part of the regulatory submission to FDA to gain approval for a product. Tr. 527:20-528:5 (Schwendeman). Pacira's PPQ batches were used to demonstrate EXPAREL®'s stability to FDA, and could be sold commercially. Tr. 414:17-416:4 (describing

stability summary for PPQ lot submitted to FDA), 451:3-22 (Schwendeman); JTX-4079.

141. Batches of commercially sold Prior Art EXPAREL® Product are "made the same way" as batches of non-commercially sold Prior Art EXPAREL® Product. Tr. 190:8-20 (Grigsby). "There [i]s no difference" between batches of commercially sold Prior Art EXPAREL® Product and non-commercially sold Prior Art EXPAREL® Product. Tr. 190:18-20 (Grigsby).

142. The '495 Patent included data from both sold and unsold batches of Prior Art EXPAREL® Product, and Pacira did not differentiate between batches that were sold and batches that were not sold. Tr. 424:8-11 (Schwendeman), 764:5-8 (Klibanov); DTX-3110; JTX-4121. For example, the named inventors included data in the patent specification from lots 16-P004, 17-3142, 17-4135, and 17-4126 as part of their representative samples of the Prior Art EXPAREL® Product. Tr. 421:19-21 (Schwendeman); JTX-4037.18. These lots were not commercially sold. Tr. 422:15-423:12 (Schwendeman); DTX-3109. However, these lots were representative of the commercial product. Tr. 190:8-20 (Grigsby).

143. The '495 Patent describes both sold and unsold batches of the 45-liter Prior Art EXPAREL as "reference samples" of EXPAREL "prepared by the current commercial process." JTX-4121.19. Pacira used these sold and unsold 45-liter "reference samples" to compare the features of the EXPAREL manufactured by the

"old" 45-liter manufacturing process against the features of the EXPAREL manufactured by the "new" claimed process. *Id*. Thus, when prosecuting the '495 Patent and seeking to distinguish the 45-liter batches from the 200-liter batches, Pacira relied on unsold 45-liter batches of Prior Art EXPAREL. *Id*.

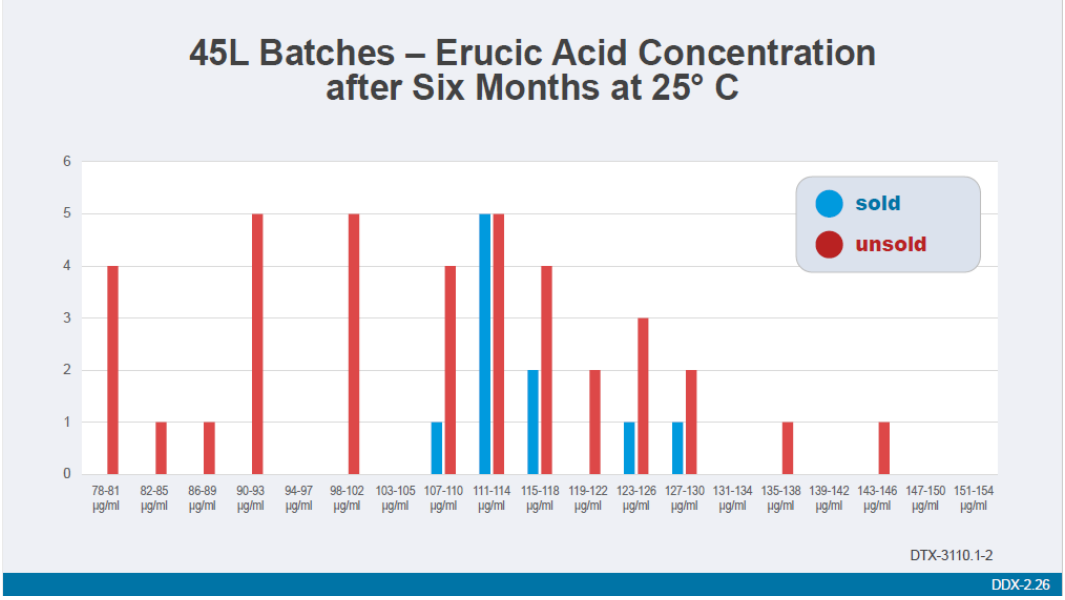
144. The range of erucic acid concentration in all forty-eight tested batches of the Prior Art EXPAREL® Product after storage at 25° C for six months was between 78 and 146 µg/mL. DTX-3110. Sixteen of the forty-eight tested batches had an erucic acid concentration of less than about 99 µg/mL (i.e., had a value up to 102 µg/mL) after six months of storage at 25° C. DTX-3110; Tr. 418:10-419:4 (Schwendeman). Of these sixteen batches, all but one "also [met] the limitation of Claim 1 and have less than 23 micrograms per milliliter or less." DTX-3110; Tr. 418:6-10 (Schwendeman).

145. Accelerated stability studies were only performed on a small number of the batches that were commercially sold. DTX-3111; Tr. 448:10-448:25 (Schwendeman). Pacira sold over 2,500 batches of the Prior Art EXPAREL® Product prior to January 22, 2021; only ten of these batches, or about 0.3%, were tested under accelerated stability conditions. Tr 452:2-123, 524:6-17 (Schwendeman); DTX-3109; DTX-3111.

146. A POSA would have understood that the actual range in erucic acid concentration under accelerated stability conditions for all commercial batches of

the Prior Art EXPAREL® Product, including batches that were not tested, was broader than the results for the limited number of batches actually tested. Tr. 447:12-448:6, 450:12-451:2 (Schwendeman); DTX-3110; DTX-3111. For example, a POSA would have understood that Pacira had manufactured thousands of batches since 2012, and that the limited data points would not reflect the breadth of the distribution of values across commercial batches. Tr. 449:1-450:16, 450:24-451:1, 452:2-12 (Schwendeman); DTX-3109. A POSA would have also understood that there was some variability in one-month erucic acid values based on these measurements. Tr. 450:11-23 (Schwendeman). A POSA would have known that the measurements themselves were approximate, because of the inherent error range in any measurement assay. Tr. 425:8-17, 434:19435:5 (Schwendeman). This broader range is confirmed by the results of the additional batches manufactured by Pacira using the same commercial-scale process that are representative of the commercially-sold batches. *Compare* DTX-3110 *with* DTX-3111; Tr. 450:11-451:2 (Schwendeman).

147. The graph below, presented at trial, illustrates the range of erucic acid concentrations after six months at 25° C in all sold and unsold batches of 45-liter EXPAREL®. DDX-2.26 (summarizing DTX-3110.1-2).



148. "It [is] about certain" that at least one batch of the Prior Art EXPAREL® Product that was commercially sold before January 22, 2021 practiced every limitation of claim 7 of the '495 Patent. Tr. 451:23-452:12 (Schwendeman).

149. Claim 7 is anticipated by EXPAREL® prepared using Pacira's 45-liter process. Tr. 383:20-24; 443:12-15 (Schwendeman).

B. OBVIOUSNESS

150. If not anticipated, the subject matter of at least claims 1 and 7 of the '495 Patent would have been obvious to a POSA in view of the Prior Art Exparel® Product and the knowledge of a POSA. Tr. 452:17-453:4 (Schwendeman).

1. Claim 1 Is Obvious

a. "a composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising"

151. It was well known in the prior art, and Pacira's witnesses admit, that the Prior Art EXPAREL® Product was a composition of bupivacaine encapsulated MVLs. DTX-2498.21; *see also* Tr. 119:23-120:9 (Hall); Tr. 183:2-185:25 (Grigsby); Tr. 443:20-24, 445:7-12 (Schwendeman); DTX-3115.

152. It was also well known in the prior art, and Pacira's witnesses admit, that the Prior Art EXPAREL® Product was sold commercially using a commercial-scale process. Tr. 94:10-12 (Hall); Tr. 183:7-9 (Grigsby); Tr. 445:7-12 (Schwendeman); Tr. 561:22-561:3 (Yaman); Tr. 781:8-11 (Klibanov (agreeing that there is no lower or upper limit to the size of a commercial scale batch)); DTX-2498 (describing the Prior Art EXPAREL® Product as being manufactured "at commercial scale").

153. It was well known that "EXPAREL . . . was commercially launched in the United States in April 2012." DTX-2078.1; *see also* JTX-4205; DTX-3109; DTX-3017. Therefore, a POSA would have understood that the Prior Art EXPAREL® Product was prepared using a "scale of manufacturing for production of a commercial product." Tr. 183:7-9 (Grisby); Tr. 445:7-446:2, 561:21-22 (Schwendeman).

b. Process steps (a)-(f) of claim 1

154. The Prior Art EXPAREL Product was prepared using the steps (a) through (f) recited in claim 1. *Supra* ¶ 110.

155. A POSA would have known to use the claimed steps set forth in limitations (a)-(f) to manufacture an MVL, and EXPAREL® in particular, because these same steps were well described in the prior art, including Pacira's own prior art patents. Tr. 557:15-562:9 (Yaman); 445:7-17, 447:2-6 (Schwendeman); JTX-4089.

c. "wherein all steps are carried out under aseptic conditions"

156. The Prior Art EXPAREL Product was prepared such that all steps (a) through (f) were carried out under aseptic conditions. *Supra* ¶¶ 110, 113.

157. A POSA would also have known to carry out the manufacturing process in aseptic conditions. The Prior Art EXPAREL® Product was known to be manufactured using an aseptic process. Tr. 119:3-9 (Hall); Tr. 185:10-16 (Grigsby); Tr. 424:16-21(Schwendeman).

d. "wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month"

158. A POSA would have understood, based on batches of the Prior Art EXPAREL® Product that were commercially available, that the Prior Art EXPAREL® Product exhibited a range of erucic acid concentrations after storage at

25° C for one month that overlapped with the range claimed in claim 1. Tr. 453:6-454:4 (Schwendeman); DTX-3110.

159. Based on Pacira's testing of commercially available batches of the Prior Art EXPAREL® Product, batches of the commercially-sold Prior Art EXPAREL® Product that underwent stability testing had a range of erucic acid concentration below 23 µg/ml after storage at 25° C for one month. Tr. 453:10-16 (Schwendeman); DTX-3110; DTX-3111.

160. Between the commercial launch of EXPAREL® in 2012 and the January 22, 2021 priority date of the '495 Patent, Pacira commercially sold nearly 2,600 batches of the Prior Art EXPAREL® Product. DTX-3109; Tr. 452:2-12 (Schwendeman).

161. Out of the thousands of batches of the Prior Art EXPAREL® Product commercially sold by Pacira between 2012 and January 22, 2021, Pacira conducted stability testing at 25° C on only a very limited number— about 0.3% of all commercially sold batches. Tr. 452:2-12, 524:6-17 (Schwendeman); DTX-3109; DTX-3111.

162. Pacira has continued to manufacture and commercially sell EXPAREL® made according to the 45-liter process (i.e., the process that was used to manufacture the Prior Art EXPAREL® Product) after January 22, 2021, and

continues to do so to this day. Tr. 163:4-5 (Grigsby); Tr. 454:9-14 (Schwendeman); JTX-4290.4 (Glenn Tr. 54:06-54:11).

163. Batches of commercially sold Prior Art EXPAREL® Product had an erucic acid concentration of "about 23 μg/ml or less" after storage at one month at 25° C. DTX-3111; Tr. 418:10-419:9 (Schwendeman). Specifically, the range of erucic acid concentrations in batches of commercially sold Prior Art EXPAREL® Product after one month of storage at 25° C was between less than 20 and 29 μg/mL. Tr. 453:11-17 (Schwendeman); DTX-3111. The claimed erucic acid range of "about 23 μg/ml or less" in claim 1 thus overlaps with the range of erucic acid a person of ordinary skill in the art would have reasonably expected for commercially sold batches of the Prior Art EXPAREL® Product. Tr. 453:10-17 (Schwendeman).

164. The claimed range ("about 23 μg/ml or less" after one month at 25° C) is not critical, and Pacira has not established that there are any unexpected results relative to the prior art range. Tr. 453:10-17 (Schwendeman).

165. A POSA would not have understood any purported difference in erucic acid concentration in the composition after one month of storage at 25° C to impact the real-time shelf life or stability, or to be a necessary timepoint. Tr. 453:6-454:14; 455:9-25, 456:13-457:6, 457:13-20; 458:9-459:16 (Schwendeman); JTX-4004; JTX-4007; JTX-4057; JTX-4264.

166. Pacira continues to sell EXPAREL® made by both its prior art 45-liter process and its "new" 200-liter process interchangeably, without identifying the manufacturing process used; and medical professionals (e.g., doctors, nurses), pharmacists or patients have (and would have) no knowledge as to which process was used to make any EXPAREL® product sold, prescribed or used. Tr. 454:9-14 (Schwendeman); JTX-4205, DTX-3115.

167. This is consistent with Pacira's representations to the FDA that the batches made using its 200-liter process are equivalent and comparable to batches manufactured using its 45-liter process. Tr. 103:8-14 (Hall); Tr. 176:12-17, 177:12-14 (Grigsby); Tr. 441:20-443:1 (Schwendeman); JTX-4053.2, .4, .6; JTX-4187.4.

168. Pacira's release testing and shelf life for EXPAREL® includes a specification of erucic acid concentration: that each batch must have a concentration of less than 310 µg/ml erucic acid. Tr. 157:23-158:1 (Grigsby); 205:10-15 (Grigsby); JTX-4159.42; JTX-4264.5. That is, Pacira has informed the FDA that any batch is acceptable for use in patients if, *inter alia*, it has a concentration of less than 310 µg/ml erucic acid. Tr. 544:6-545:12 (Schwendeman); JTX-4264.5. Thus, the one-month erucic acid concentration levels at 25° C do not matter for any practical purpose. Tr. 456:14-458:11 (Schwendeman); JTX-4057.29; JTX-4264.5. As long as the erucic acid concentration is below 310 µg/mL for the two-year shelf

life, there is no impact on pharmacokinetics and product performance. Tr. 458:3-11 (Schwendeman).

169. The FDA-approved label for EXPAREL® (e.g., the 2018 EXPAREL Label and 2023 EXPAREL Label) indicates that it should be stored under refrigerated conditions. Tr. 154:20-22 (Grigsby); Tr. 403:5-10 (Schwendeman); JTX-4205; DDX-3115.

2. Claim 7 Is Obvious

170. Claim 7 depends from claim 1, and requires that the erucic acid concentration in the composition is "about 99 µg/mL or less after the composition is stored at 25° C for six months." JTX-4121; Tr. 391:18-392:2 (Schwendeman).

171. Batches of the Prior Art EXPAREL® Product had an erucic acid concentration of about 99 µg/mL or less after the composition was stored at 25° C for six months. DTX-3110. Batches of tested, commercially sold Prior Art EXPAREL® Product had a erucic acid concentration after storage at 25° C for six months that ranged between about 110 to 127 µg/mL. Tr. 449:1-9 (Schwendeman); DTX-3111.

172. At most, the difference between the range of erucic acid concentration in batches of tested, commercially sold Prior Art EXPAREL® Product and the claimed range is less than 11 µg/ml (110 minus 99). Tr. 453:13-2- (Schwendeman); DTX-3111. 11 µg/mL is equal to about 0.35% DEPC degradation in the MVL lipid

membrane. *See* JTX-4264.5 (Pacira's NDA documentation, disclosing to FDA that 310 µg/mL is equivalent to 10% degradation of DEPC in EXPAREL); Tr. 458:7-22 (Schwendeman); Tr. 191:22-192:24 (Grigsby) (confirming that an increase of 15 µg/mL erucic acid would be "about half a percent of DEPC hydrolysis").

173. A POSA would have understood, based on batches of the Prior Art EXPAREL® Product that were commercially available, that the difference between the range of erucic acid concentrations in the Prior Art EXPAREL® Product after storage at 25° C for six months and the claimed range of "about 99 µg/mL or less" is so small that a POSA would have reasonably expected them to have the same properties. Tr. 418:24-419:4, 453:17-459:16 (Schwendeman); DTX-3111.

174. A person of ordinary skill in the art would not have expected the difference between the range of erucic acid after storage at 25° C for six months in the tested, commercially sold Prior Art EXPAREL® Product, and the claimed range of "less than about 99 µg/mL," to have an impact on the properties of EXPAREL®, including release rate of bupivacaine and pharmacokinetics. JTX-4264.5; Tr. 459:11-16 (Schwendeman).

175. Pacira's release and shelf life testing for EXPAREL® includes a specification for erucic acid concentration: that each batch must have a concentration of less than 310 µg/ml erucic acid. Tr. 157:23-158:1, 205:10-15 (Grigsby); Tr. 457:13-16 (Schwendeman); DTX-2498.42; JTX-4057.29.

176. Pacira admitted to FDA that batches of EXPAREL with up to 310 µg/mL of erucic acid "was observed to have no affect [sic] on the in vitro release of" the drug product, and that "product with erucic acid values up to 310 µg/mL will maintain product performance." JTX-4264.5. Pacira's FDA filings state that the specification of no more than 310 µg/mL is based on this finding: that there is no difference in the product's performance when the erucic acid levels remain below 310 µg/mL. JTX-4264.5. "From the FDA perspective . . . whether you're above or below 99 micrograms per milliliter" is not important, because "[i]f you are below 310, then the product could be used. It's within specification for shelf life." Tr. 457:13-20 (Schwendeman).

177. All batches of EXPAREL have the same shelf life of two years at refrigerated conditions. Tr. 454:6-15 (Schwendeman); Tr. 767:9-14 (Klibanov); JTX-4205; DTX-3115.

178. Accordingly, a POSA would have "expect[ed] that batches after six months of storage at 25 degrees C with 99 micrograms per milliliter of erucic acid would have the same or similar properties as ones with 110 to 115 micrograms per milliliter." Tr. 453:24-454:5, 459:11-16 (Schwendeman).

179. The six-month erucic acid levels at 25° C do not matter for any practical purpose. Tr. 453:6-454:14, 455:9-25, 456:15-457:6, 457:13-20; 458:9-459:16 (Schwendeman).

180. The six month erucic acid levels at 25° C are not predictive of shelf life. Pacira's expert agrees that "Pacira concluded it wasn't six months at 25 degree Celsius that corresponded with the shelf life of the product. It was two or three months," and that for the EXPAREL® product, "what the Arrhenius correlation predicts is two or three months at 25 degree Celsius will correlate with 24 months at 5 degree Celsius." Tr. 769:1-770:4 (Klibanov); *see also* JTX-4004; JTX-4007; JTX-4057; JTX-4264.

181. As long as the erucic acid concentration is below 310 µg/mL for the two-year shelf life, there is no impact on pharmacokinetics and product performance. Tr. 458:3-11 (Schwendeman); JTX-4264.5. There is no meaningful difference in the shelf life of the product due to a slightly lower erucic acid concentration after storage at 25° C for six months; the shelf life is two (2) years regardless of any difference in the erucic acid concentration under accelerated stability conditions. Tr. 454:6-8 458:25-459:1 (Schwendeman); JTX-4057.29; JTX-4264.5.

182. Pacira continues to sell product made by both its prior art 45-liter process and its 200-liter process interchangeably, without identifying the manufacturing process used; and medical professionals (e.g., doctors, nurses), pharmacists or patients have (and would have) no knowledge as to which process was used to make any EXPAREL® product sold, prescribed or used. Tr. 454:9-14 (Schwendeman (adding that "[w]hen I buy vials at the University of Michigan

hospital pharmacy for my research, I do not know if it's 45 liter or 200 liter.")); JTX-4205; DTX-3115. This too confirms that there is no meaningful difference between the products.

183. This is consistent with Pacira's representations to the FDA that "[t]he stability profile of 20 Ml EXPAREL registration lots manufactured using the 200 L bulk manufacturing process is comparable to other EXPAREL lots on the stability program manufactured at 45 L scale," that "the increase in erucic acid are [sic] consistent with EXPAREL lots on the stability program manufactured at the 45 L scale over 6 months," that "[t]he trend [in pH value decrease over 6 months] is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25 ± 2°C)"; and that "[t]he stability data collected over nine months from Exparel registration lots manufactured with the 200-liter bulk manufacturing process at Swindon confirm the material is equivalent to the drug product manufactured by the approved 45-liter process." JTX-4187.4; *see also* Tr. 442:7-443:1 (Schwendeman)

184. A POSA would have understood the Prior Art EXPAREL® Product to practice all the limitations of claim 7. Tr. 452:17-24 (Schwendeman). And Pacira has not presented any evidence that the prior art teaches away from the subject matter recited in claim 7. To the extent there are any differences between the erucic acid in the Prior Art EXPAREL® Product after six months of storage at 25° C and the

claimed range, they are so small that a POSA would have reasonably expected the claimed composition to have the same properties as the prior art. Tr. 453:24-454:4 (Schwendeman).

C. SECONDARY CONSIDERATIONS DO NOT OVERCOME THE *PRIMA FACIE* CASE OF OBVIOUSNESS

185. Even if Pacira's assertions of secondary considerations were credited, they would not overcome the strong case of *prima facie* obviousness present here. Moreover, Pacira's assertions of secondary considerations are flawed on their own terms.

1. Pacira Fails to Establish Any Skepticism

186. Pacira has failed to establish that there was any skepticism in the field regarding the ability to manufacture a bupivacaine encapsulated MVL with the claimed erucic acid concentrations. Pacira attempted to establish that the inventors (Pacira employees) were skeptical of success through the testimony of Mr. Hall; however, Mr. Hall admitted that he actually had ***greater*** skepticism regarding the spray process, as compared to the 200 liter process. Tr. 114:6-116:20 (Hall (agreeing that he had previously testified under oath that "I think the lower risk option was always going to be the 200-liter and the pie-in-the-sky was going to be spray.")).

2. Pacira Fails to Provide Evidence of Unexpected Results

187. For unexpected results to be relevant to an evaluation of obviousness, there must be evidence that the results are, in fact, unexpected. *See* COL ¶ 66-70. There is no evidence that the results are unexpected.

188. If the Examiner had been presented with the full accelerated stability data on all tested batches, it would have been apparent that the data is highly variable for both the 45-liter and 200-liter batches, and that there is an overlap for the measured values for the 45-liter and 200-liter batches. Tr. 447:12448:6, 450:11-23, 453:17-24, 462:11-20, 490:8-15 (Schwendeman); DTX-3110; DTX-3111.

189. For unexpected results to be relevant to an evaluation of obviousness, the results must show a difference in kind, rather than just a difference in degree. *See* COL ¶ 66-70. To the extent there is any difference (and there is not here), this is not a difference in kind. *See supra* ¶¶ 172-79.

190. For unexpected results to be relevant to an evaluation of obviousness, the results must also be commensurate with the claim scope. *See* COL ¶ 66-70. To the extent any unexpected results actually exist (they do not), they are not commensurate with the scope actually claimed by the patent. There are no unexpected results that are commensurate with the scope of claim 7. Tr. 460:1-8 (Schwendeman).

191. Claim 7, which is generally directed to compositions "prepared by a commercial scale process," is not directed to any limit on the volume of the scale of the manufacturing process or any other aspect of the manufacturing, e.g., mixing speed, mixing time, volume of raw materials, specific solvents, microfiltration scale. Tr. 567:3-6 (Schwendeman); Tr. 569:6-13, 572:3-10 (Yaman); JTX-4121.

192. Although Pacira now claims that the unexpected results stem from the levels of lysine and the pH values, lysine levels and pH values are not recited in claim 7. JTX-4121.

193. In Pacira's statements to the FDA seeking approval to sell EXPAREL manufactured through Pacira's 200-liter process, Pacira did not represent that increased lysine or pH could (much less did) impact the level of erucic acid or in vitro release of bupivacaine from the MVL. Tr. 545:7-546:10 (Schwendeman); JTX-4264.5. And named inventor Dr. Grigsby admits that Pacira does not use different concentrations of lysine when manufacturing the 200-liter batches versus the 45-liter batches. Tr. 167:7-12 (Grigsby).

194. The lysine values that Pacira provided to the FDA were not the same as what Pacira provided to the USPTO and included in the '495 Patent; Pacira is unaware of whether the lysine data in the '495 Patent specification is accurate. Tr. 199:4-200:6 (Grigsby); *see also* Tr. 460:9-15 (Schwendeman).

195. Unexpected results should not be evaluated based on a comparison of average erucic acid concentrations because claim 7 is not directed to batches with an ***average*** erucic acid concentration under accelerated stability conditions for six months. JTX-4121.

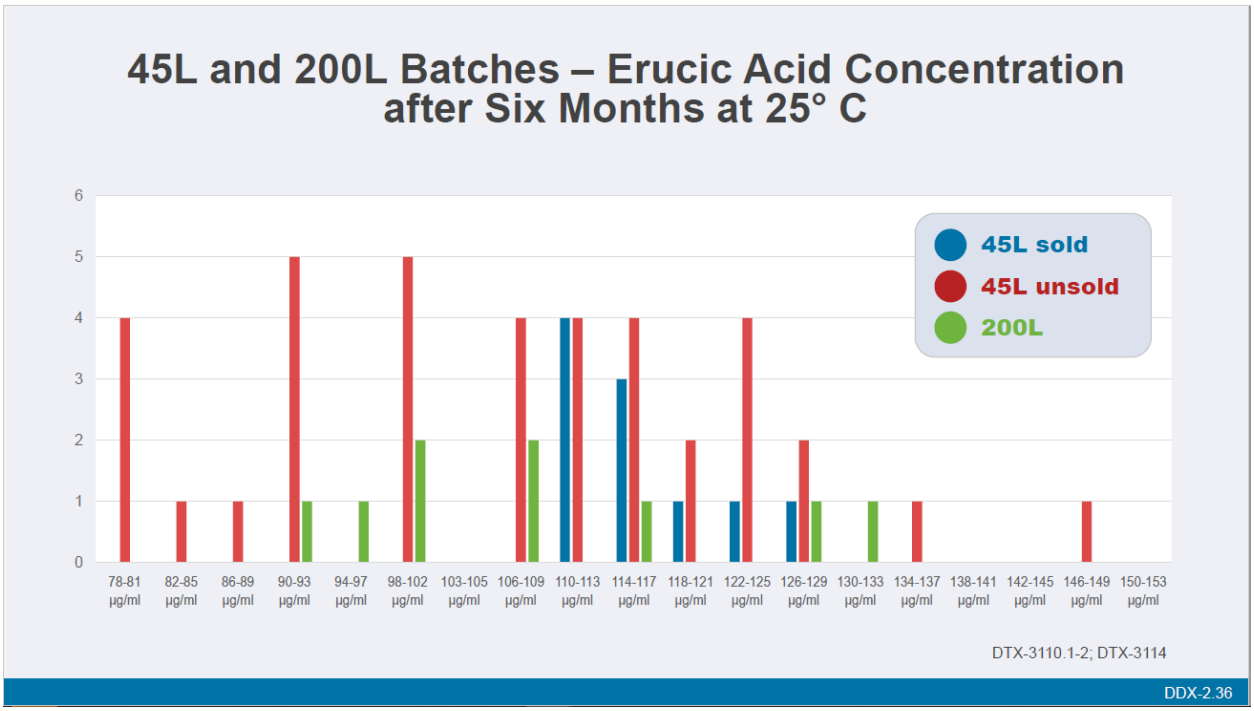
196. As explained above, fifteen batches of the forty-eight batches of 45-liter EXPAREL tested after six months storage at 25° C had an erucic acid concentration of both about 23 μg/mL or less after one month of storage, and about 99 μg/mL or less after six months of storage. *Supra* ¶¶ 114. Thus, about 31% of the tested batches of 45-liter EXPAREL met the limitations of claim 7.

197. Similarly, only four of the nine tested 200-liter EXPAREL batches (batch numbers 129855, 129856, 129860, and 120862) had an erucic acid concentration of both about 23 μg/mL or less after one month of storage, and about 99 μg/mL or less after six months of storage. DTX-3114. And as described above, none of the tested commercially sold batches of 200-liter EXPAREL® (batch numbers 21-2001, 21-2002, and 21-2003) met the erucic acid concentration limitations of claim 7. *See supra* ¶ 102.

198. As described above, the 45-liter process produced batches of EXPAREL with a range of erucic acid concentrations after six months storage at 25° C. *Supra* ¶ 97. The 200-liter process also produced batches of EXPAREL® with a range of erucic acid concentrations after six months storage at 25° C. Tr. 462:11-20

(Schwendeman). "There is no difference" between the six month accelerated stability erucic acid concentrations in batches made at 45-liter scale and 200-liter scale. Tr. 462:16-18 (Schwendeman).

199. The visual below illustrates that there is no difference in the range of erucic acid concentrations after storage at 25° C for batches of EXPAREL® produced at the "old" 45-liter scale or "new" 200-liter scale. DDX-2.36 (summarizing DTX-3110.1-2; DTX-3114).



200. Therefore, there are no differences between the closest prior art (i.e., the Prior Art EXPAREL® Product) and the claimed composition with respect to the erucic acid concentration under accelerated stability conditions for six months.

3. Pacira Fails to Provide Evidence of Any Long-Felt, Unmet Need

201. In order to be relevant to an evaluation of obviousness, any long-felt, unmet need should be a need created by inadequacies in the technical knowledge, not one due to business-driven market forces. *See* COL ¶ 84. The purported long-felt, unmet need identified by Dr. Klibanov—"an urgent need for new and improved large-scale productions of EXPAREL® to meet the substantial and growing market demand"—and described in the '495 Patent has nothing to do with any technical considerations. Tr. 727:5-15 (Klibanov); JTX-4121.10 (1:32-36). Mr. Hall testified that Pacira's development of its 200-liter process was solely to accommodate a purported increase in market demand for EXPAREL®—this is a business-driven market consideration, and does not establish a long-felt, unmet need for purposes of evaluating obviousness. Tr. 93:12-94:6 (Hall).

202. Other than statements from the '495 Patent's specification, Pacira did not present any evidence that any such "unmet need" was actually long-felt. *See, e.g.*, Tr. 726:11-17, 726:22-726:10 (Klibanov). Self-serving statements in the patent specification are not reliable evidence to show that there was any long-felt, unmet need. *See* COL ¶ 82-89.

203. Even if there was a need for a "larger-scale production of stable EXPAREL," one reason why such a need existed would have been because of Pacira's own prior art patents. *See* Tr. 339:6-340:1 (Molloy). The '838 Patent,

which expired in 2021 but was listed in the Orange Book for EXPAREL until its expiration, described a commercial scale process for manufacturing multivesicular liposomes, using the same general steps recited in claim 1 of the '495 Patent. JTX-4089.37-38; JTX-4121.11 (4:31-35) ("the current process used for the manufacturing of Exparel®, which is disclosed in U.S. Pat. No. 9,585,838 and is incorporated by reference in its entirety"); Tr. 562:3-15 (Yaman); DTX-2019. The '838 Patent states that "[t]his process is suitable for manufacturing at commercial scales." JTX-4089.21 (3:28-29). If there was any long-felt, unmet need for "larger-scale productions of stable EXPAREL," the only reason that need was purportedly not met is because of Pacira's blocking patents.

204. Furthermore, Pacira admitted at trial that in the past, it had successfully increased production of EXPAREL® by building more 45-liter scale manufacturing lines. Tr. 93:9-17 (Hall). The "main reason" that Pacira did not continue to build more 45-liter manufacturing lines was because of "operational complexity" requiring "a lot of oversight," which Mr. Hall testified was "not really something we're interested in doing." Tr. 94:19-95:9 (Hall).

D. CLAIM 7 IS INVALID FOR LACK OF ENABLEMENT

205. Claim 7 of the '495 Patent is directed to the composition of claim 1, "wherein the erucic acid concentration in the composition is about 99 μg/mL or less after the composition is stored at 25° C. for six months." JTX-4121.20-21. Claim

1 of the '495 Patent is directed to a composition produced using a commercial scale process, using a series of process steps (a) through (f) under aseptic conditions to yield a composition of bupivacaine encapsulated MVLs "wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month." JTX-4121.20. Claim 7 is not enabled because there would be undue experimentation involved to make the full scope of the claimed compositions, including the claimed one-month and six-month erucic acid concentrations, and therefore the claim is invalid under 35 U.S.C. § 112(a).

1. Breadth of the Claim

206. Claim 7 is broadly directed to a composition of bupivacaine encapsulated MVLs prepared using a commercial scale process, using certain process steps (a) through (f) under aseptic conditions, having an erucic acid concentration in the composition of about 23 μg/mL or less after the composition is stored at 25° C for one month, and an erucic acid concentration of about 99 μg/mL or less after the composition is stored at 25° C for six months. JTX-4121.21; Tr. 569:5-16 (Yaman); Tr. 389:2-391:5 (Schwendeman); Tr. 290:25-291:8 (Karaborni).

207. The Court has construed the term "commercial scale" as "a scale of manufacturing for production of a commercial product." D.I. 187 at 17. Claim 7 is not limited to a composition prepared by a specific volume, or even or range of volumes for the final aqueous suspension produced from the commercial scale

process. JTX-4121.21; Tr. 568:4-7, 569:10-13 (Yaman); Tr. 779:20-25 (Klibanov (agreeing that there is "[n]o volume limitation at all in commercial scale")).

208. In contrast, Pacira has claims in other patents within the same patent family that are directed to use of a specific range of volume produced from the process. For example, claim 18 of U.S. Patent No. 11,278,494 is directed to a composition "prepared by a commercial process having a final product volume of about 200 L to about 225 L." JTX-4130.23; Tr. 568:18-569:13 (Yaman). Claim 17 of U.S. Patent No. 11,357,727 is directed to a composition in which the "final aqueous suspension of bupivacaine encapsulated MVLs has a volume of about 200 L to about 225 L." JTX-4009.23.

209. Claim 1 recites certain product-by-process limitations (a)-(f) relating to the process used to manufacture the composition. JTX-4121. 20-21; Tr. 557:13-561:23, 569:14-570:16 (Yaman); Tr. 118:5-119:16 (Hall); Tr. 182:21-185:25 (Grigsby); Tr. 731:5-733:8 (Klibanov). Although claims 1 and 7 recite that the composition must have a certain stability as measured by erucic acid concentration after storage at 25° C for one month and six months, the claims do not recite any specific process parameters that must be used to prepare a composition that would have the required erucic acid concentrations. JTX-4121.20-21; Tr. 570:17-24 (Yaman); Tr. 798:14-802:11, 803:22- 813:6 (Klibanov).

210. Step (a) of claim 1 recites a step for "mixing a first aqueous solution," but is not limited to use of a "high shear mixer" for this step. JTX-4121.20. Dependent claims 9-11 of the '495 Patent are directed to use of a "high shear mixer" for step (a), thus making clear that step (a) of claim 1 is broader and also includes use of a "low shear" mixer. JTX-4121.21. The '495 Patent specification states that "[i]n some embodiments of the process described herein, the mixing in step (a) is performed using a first mixer at a high shear speed." JTX-4121.13 (7:53-55). Thus, the specification makes clear that the mixing in step (a) is not limited to use of "high shear" mixing.

211. Dr. Klibanov's testimony that he did not believe step (a) covered both "high shear" and "low shear" mixing (Tr. 804:12-23 (Klibanov)) is contrary to the principles of claim differentiation, and would improperly read embodiments from the specification into the claim.

212. Step (b) of claim 1 recites a step for "mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion," but is not limited to use of a "low shear mixer" for this step. JTX-4121.20. Dependent claims 13-15 of the '495 Patent are directed to use of a "low shear mixer" for step (b), thus making clear that step (b) of claim 1 also includes use of a "high shear" mixer. JTX-4121.21.

213. Claims 1 and 7 are not limited to use of any particular liquid volume to be used for the first and second emulsion steps. 572:3-10 (Yaman); Tr. 800:16-19 (Klibanov).

214. Claims 1 and 7 are not limited to use of any specific type of impeller, mixer speed, mixing time, or temperature for forming the first and second emulsions. JTX-4121.20-21.

215. Claims 1 and 7 do not limit the particular gas flow rate or geometry of the sparge configuration to be used for the solvent removal step, step (c). JTX-4121.20-21.

216. Claims 1 and 7 broadly recite use of general unit operations for manufacturing MVL compositions, but do not recite the specific process parameters that should be used to yield a product that has the claimed stability. JTX-4121.20-21.

2. Nature of the Alleged Invention

217. Claim 7 is generally directed to compositions of bupivacaine encapsulated multivesicular liposomes prepared by a commercial scale process, using a series of process steps, with a certain stability profile as measured by erucic acid concentration. JTX-4121.10, 21; Tr. 118:5-119:9 (Hall); Tr. 183:2-185:25 (Grigsby); Tr. 568:15-570:16 (Yaman); Tr. 390:2-392:2 (Schwendeman); Tr. 731:5-733:14 (Klibanov).

218. The subject matter of claim 7 was already known in the prior art. *Supra* Section II.A (Anticipation). To the extent claim 7 is directed to an "invention," the alleged nature of the "invention" recited in claim 7 is a bupivacaine MVL formulation with improved stability as measured by erucic acid concentration after storage stored at 25° C for one month and six months. Tr. 569:14-570:16 (Yaman); Tr. 460:1-5 (Schwendeman).

3. State of the Prior Art

219. The prior art disclosed the general process for making MVLs, and specifically for making MVLs with bupivacaine. Tr. 557:15-562:15 (Yaman); Tr. 736:12-737:18 (Klibanov); JTX-4089; JTX-4202. The process steps (a) through (f), recited in claim 1 of the '495 Patent, were known in the prior art literature. JTX-4089; JTX-4202; Tr. 557:13-562:15 (Yaman); Tr. 800:24-801:2 (Klibanov). For example, a 2002 article titled "A lipid based depot (DepoFoam® technology) for sustained release drug delivery," disclosed a double-emulsion manufacturing process to make MVLs. JTX-4202 ("Mantripragada"). Mantripragada discloses more specifically that:

> The first step is making a "water-in-oil" emulsion by dissolving amphipathic lipids containing at least one neutral lipid in one or more volatile organic solvents for the lipid component, adding to the lipid component an immiscible first aqueous component and a biologically active substance to be encapsulated. The mixture is then emulsified, and then mixed with a second immiscible aqueous component followed by mechanical mixing to form solvent spherules suspended in the second aqueous component. The solvent spherules contain multiple

> aqueous droplets with the substance to be encapsulated dissolved in them. The organic solvent is removed from the spherules, generally by evaporation, by reduced pressure or by passing a stream of gas over or through the suspension. When the solvent is completely removed, the spherules become MVLs.

JTX-4202.6-7.

220. Mantripragada also discloses that the MVL particles should be filtered and concentrated. *Id.* at 6 (disclosing microfiltration for "concentration of DepoFoam particles while exchanging saline storage solution for buffer and unencapsulated materials," followed by "[a]djustment of potency to final product concentration"). Mantripragada also discloses that aseptic process technique should be used. *Id.* at 8.

221. U.S. Patent No. 9,585,838 ("the '838 patent") also disclosed the double-emulsion process, as recited in claim 1 of the '495 Patent. Tr. 557:15-562:15 (Yaman); Tr. 736:12-737:18 (Klibanov). The '838 patent issued on March 17, 2017, and was assigned to Pacira. JTX-4089.1; Tr. 562:8-15 (Yaman). The '838 patent discloses process for making MVLs "suitable for manufacturing at commercial scales." JTX-4089. 21. The '838 patent discloses a double-emulsion a process for making MVLs, using the steps recited in claim 1 of the '495 Patent. JTX-4089.21; Tr. 557:15-562:15 (Yaman); Tr. 800:24-801:2 (Klibanov). The '838 patent discloses a solvent removal step followed by a series of concentration/filtration steps, as recited in claim 1 of the '495 Patent. JTX-4089.21; Tr. 560:19-561:6

(Yaman). The '838 patent also discloses that the process can be carried out aseptically. JTX-4089.21.

222. Pacira has been using the process steps (a) through (f) recited in claim 1 of the '495 Patent, that were known in the prior art literature, to manufacture EXPAREL® since 2012. Tr. 118:5-119:9 (Hall (agreeing that "[t]he 45-liter process uses all of those steps, A through F")); Tr. 183:2-185:25 (Grigsby (agreeing that limitations (a)-(f) of claim 1 "is the same between the 45-liter and 200-liter process)); Tr. 445:15-446:2, 447:3-6 (Schwendeman); Tr. 557:13-562:9 (Yaman); JTX-4174.1.

223. Although the general process steps to manufacture MVLs were well known in the prior art, MVLs remained challenging to manufacture. Tr. 179:11-14 (Grigsby ("Exparel manufacturing is incredibly complex.")); Tr. 476:5-12 (Schwendeman (agreeing that "EXPAREL itself" is "definitely [a] complex product" because "[i]t has a complex manufacturing")); Tr. 584:9-20 (Yaman (agreeing that "[t]he manufacturing process required to form the MVLs that comprise EXPAREL is a very complex and involves multiple emulsion steps that must be performed under precisely controlled conditions")); Tr. 724:2-6 (Klibanov (agreeing that "[l]arge-scale manufacturing of MVL is a complex and marathon task.")). For example, a 2017 review article, published in the American Association of Pharmaceutical Scientists ("AAPS") Journal, states that "[d]espite the popularity

of the liposome platform, developability, manufacturability, scalability, and stability are key challenges with the technology. These challenges are due to the fact that liposomal products are complex formulations in which (lipid) excipients play a critical role in product performance." JTX-4210.1-2; Tr. 723:1-10 (Klibanov). The article further states that "[t]he manufacturing process used to produce a liposomal product may significantly influence its quality and performance." JTX-4210-3. Further, "[i]rrespective of the process adopted for manufacturing liposomes, it is important to understand the process and impact of critical process parameters on product quality and safety through prior knowledge and/or risk assessment techniques. This understanding is fundamental in order to have a robust process in place that gives batch-to-batch reproducibility and maintains product quality irrespective of small deviations in the process parameters." *Id.* The authors concluded that "a thorough understanding of the manufacturing process and the use of appropriate in-process controls result in a well-controlled manufacturing process that is less likely to experience failures during scale-up." *Id.* at 8.

224. An article published in 2022 reports that although "[t]he double emulsification process is a widely used technique that involves multiple processing steps that require strict maintenance of all feed streams," "[t]he production of MVL continues to be a challenge because it lacks batch-to-batch reproducibility, longer processing time, residual organic solvents, an effective sterilization process, and the

necessity to perform the entire process in an aseptic environment." JTX-4230.3. The authors further state that "[l]arge-scale manufacturing of MVL is a complex and marathon task due to the unique characteristic of this dosage form and critical unit operations," that "[p]roper understanding of the mechanism of particle formation, the rationale for using each composite, and effective and efficient use of equipment/techniques are essential." *Id.* at 4.

225. The prior art did not disclose what process parameters would impact accelerated stability as measured by erucic acid concentration after storage. Tr. 563:15-18, 585:21-24 (Yaman); Tr. 800:24-801:5 (Klibanov). Dr. Klibanov agreed with Dr. Yaman that none of the prior art, including Mantripragada and the '838 patent, specifically discloses what parameters would impact erucic acid concentration under accelerated stability conditions. Tr. 802:5-14 (Klibanov).

4. Working Examples and Amount of Direction Provided in the Specification

226. The specification of the '495 Patent does not provide adequate guidance to have enabled a POSA to manufacture the full scope of claimed compositions recited in claim 7 without undue experimentation. Tr. 571:12-574:9 (Yaman).

a. The '495 Patent Provides No Working Examples of How to Make a Composition that Would Practice Claim 7

227. The specification provides only two Examples. Neither Example provides the actual process conditions on how to make a composition that would practice claim 7 of the '495 Patent. Tr. 572:22-24 (Yaman).

228. Example 1 notes that the "lipid stability of three batches (Batch No. 1, 2 and 3 in Tables 1A and 1B) of bupivacaine MVLs aqueous suspension prepared by the new process described herein . . . were compared to ten reference samples of bupivacaine MVLs aqueous suspension prepared by the current commercial process." JTX-4121.19. The Example provides erucic acid concentration and pH values at 1 month, 2 month, 3 month, and 6 month time points for Batch 1, 2, and 3. *Id.*

229. Example 1 does not identify the scale of the process that was used to produce the bupivacaine MVL compositions. JTX-4121.19; Tr. 571:24-572:10 (Yaman); Tr. 117:8-12 (Hall). Example 1 provides results from one "new process," but does not identify the commercial scale that was used. JTX-4121.19; Tr. 571:24-572:10 (Yaman). Example 1 provides stability data for a product produced at one scale, and does not provide information on any additional batches prepared according to the full breadth of "commercial scale" processes that fall within the scope of claim 1. JTX-4121.19.

230. Example 1 does not identify the volume of the first and emulsion steps that were used to make Batches 1, 2, and 3. JTX-4121.19; Tr. 571:24-572:7 (Yaman).

231. Example 1 does not identify ***any*** process parameters used to manufacture the MVL compositions that allegedly have the claimed erucic acid concentration under accelerated stability conditions. JTX-4121.19; Tr. 563:15-18 (Yaman); Tr. Tr. 772:5-13 (Klibanov). Assuming that the MVL compositions were in fact prepared using the steps recited in steps (a)-(f) of claim 1, Example 1 does not provide any details at all on any process parameters used for each step. JTX-4121.19; Tr. 563:15-18 (Yaman); Tr. 772:5-13 (Klibanov).

232. Example 2, titled "Measurement of Lysine and Dextrose Concentrations in Bupivacaine MVLs," provides results for lysine and dextrose concentrations for Batches 1, 2 and 3. JTX-4121.19. Example 2 does not identify the volume of the first and second emulsion steps that were used to make Batches 1, 2, and 3. JTX-4121.20; Tr. 572:11-24, 582:18-20 (Yaman).

233. Example 2 does not identify any process parameters used to manufacture Batches 1, 2, and 3. JTX-4121.20; Tr. 572:11-24, 581:12-24 (Yaman); Tr. 800:16-19 (Klibanov).

234. Example 2 states that "[t]he higher internal pH of the bupivacaine MVL particles . . . may be attributable to the higher lysine concentration inside the MVL

particles," and that "the slight increase in MVL internal pH may also contribute to the stability of the lipid membranes." JTX-4121.20. This is a hypothesis only; the patent specification does not provide any proof that, in fact, a higher lysine concentration leads to higher internal pH inside the MVLs, and is therefore responsible for increased stability. Tr. 572:11-574:9 (Yaman); Tr. 460:9-15 (Schwendeman). Nor was any such proof (or even evidence) offered at trial.

235. The patent specification does not explain how the lysine concentration results reported in Example 2 were measured, or how the samples were prepared in order to obtain such a measurement. JTX-4121.20.

236. Pacira did not offer any evidence at trial from a witness who was personally familiar with the lysine testing reported in the patent specification. Dr. Grigsby testified that he was not familiar with the precision and accuracy of the assay used by Pacira to measure lysine. Tr. 188:12-189:17 (Grigsby).

237. The patent specification does not explain how the lysine concentration inside the MVLs can be increased. Tr. 573:22-574:9 (Yaman). Dr. Grigsby testified that because of the "different mixing dynamics" for Pacira's 200-liter process, more lysine is incorporated within the MVLs. Tr. 167:23-168:7 (Grigsby). The specification, however, does not disclose the "mixing dynamics" that were used for Pacira's 200-liter process that would result in a composition that would practice claim 7. Furthermore, Pacira has made numerous batches at 200-liter commercial

scale that did not practice claim 7, reinforcing that the "mixing dynamics" required to practice claim 7 are not known, much less disclosed in the patent specification. Tr. 460:24-462:20 (Schwendeman (explaining that, for "all the 200-liter data, there is a very large range as well from - some are 92 to 133" µg/mL of erucic acid after six months storage at 25 C)); DTX-3114.

b. The Remainder of the Patent Specification Does Not Provide Adequate Guidance on How to Practice the Full Scope of Claim 7

238. The remainder of the patent specification does not provide adequate detail that would have enabled a POSA to manufacture the full scope of claimed compositions recited in claim 7 without undue experimentation. Tr. 554:5-8, 590:21-591:2 (Yaman).

239. The specification does not identify the process parameters that were used to make Batches 1, 2, and 3 described in the '495 Patent specification. Tr. 563:1-18, 571:16-572:10 (Yaman); Tr. 806:19-807:2 (Klibanov). Although the patent specification discloses a range of mixing speeds, times, and blade diameters that could be used (JTX-4121.13), the patent specification does not identify what mixing speeds, times, and blade diameters that were actually used to make Batches 1, 2, and 3. Tr. 574:16-575:14 (Yaman); Tr. 807:19-808:7 (Klibanov).

240. The patent specification does not identify the volume of the first and second emulsion steps. Tr. 572:3-7 (Yaman); Tr. 800:16-19 (Klibanov).

241. The patent specification provides a range of mixing speeds, blade diameters, and mixing times for the first and second emulsion steps. JTX-4121.13 For the first emulsion step, the patent specification discloses a range of mixing speed from 1100 to 1200 rpm, 65-75 minutes, and a blade diameter of 8 to 10 inches. *Id.* For the second emulsion step, the patent specification discloses a range of mixing speed from 450 to 510 rpm, 60-65 seconds, and a blade diameter of 10 to 14 inches. *Id.*

242. The disclosure in the patent of a range of mixing speeds, mixing time, and blade diameters is not sufficient to have enabled a POSA to make a composition that would practice claim 7 without undue experimentation. Tr. 585:25-589:20 (Yaman).

243. Although the specification describes embodiments of various speeds with mixers, the description of speeds is insufficient without additional details on the type of mixer, size of mixer, and the vessel size and configuration. Tr. 575:23-576:15 (Yaman (explaining that "[T]here's more that goes into mixing than just the blade speed and the size of the blade. You have to take into consideration all the attributes that's required to create the dynamic situation inside the vessel. So you need to know the design of the vessel, the - what I like to refer to as the geometry of the vessel.")). For example, whether or not a given speed results in a "high" or "low" shear will depend on more than just the speed—one would need to know the type

and size of the mixer and the vessel size and configuration, but the specification does not provide this detail. Tr. 575:20-576:15, 579:2-5 (Yaman). The specification does not provide any information on the size of the vessels used for the emulsion steps, or the geometry of the vessel, or height of the mixer in the liquid. Tr. 581:18-582:24 (Yaman). As Mr. Hall admitted, the specification does not identify the liquid height or the mixer height used by Pacira. Tr. 123:12-25 (Hall). Mr. Hall also admitted that the liquid height and mixer height will impact the size of the liposome particles, and that a different blade diameter would require a different mixing speed. Tr. 122:24-8 (Hall). Mr. Hall also admitted that the vessel geometry will impact the mixing performance, and that for a fixed blade diameter, the process may not even work if the vessel geometry is not correct. Tr. 122:10-15 (Hall). Notably, Pacira had internal documents that provided the details on its vessel geometry, blade height, and type of mixer, but Pacira chose not to include any of that information in the patent. Tr. 123:3-125:17 (Hall); Tr. 582:12-14 (Yaman); JTX-4148.27-28

244. The specification does not provide any analysis of the impact of the mixing speeds, blade diameter, and mixing time on the erucic acid concentration after storage at 25° C. Tr. 576:24-577:3 (Yaman).

245. Dr. Grigsby testified that Pacira's 200-liter process had different "mixing dynamics" because it used a "new vessel with two mixers and much larger volume." Tr. 166:17-21 (Grigsby). The specification, however, does not disclose

the "mixing dynamics" used for the 200-liter process, nor does it disclose the volume of the vessels used by Pacira, or even that Pacira used a single vessel with two different mixers for the first and second emulsion steps. Tr. 582:12-14 (Yaman); Tr. 809:20-810:10 (Klibanov).

246. The specification does not provide detail on the type of mixer that should have been used in the emulsion steps to manufacture an MVL composition with the claimed stability. Tr. 580:20-24 (Yaman). A POSA would have understood that there are many different types of mixers. Tr. 580:25-581:3 (Yaman). For its 200-liter process, Pacira used what is called a Cowles blade, a type of impeller, but this detail is not reported in the specification. JTX-4188.7; Tr. 811:2-16 (Klibanov).

247. The patent specification also states that "[i]n further embodiments, the first mixer used in step (a) of the process is not a static mixer." JTX-4121.18. Thus, some embodiments of claim 1 can include use of a static mixer. The specification does not provide any information at all on the process parameters (including flowrate, pipe diameter, and baffle geometry) to be used for a static mixer to yield a product with the claimed stability. *See* Tr. 575:23-576:15 (Yaman).

248. The specification does not explain how "low shear" mixing could be used in the first emulsion step to form the water-in-oil emulsion. Dr. Klibanov testified that "high shear" mixing was "required" for the first emulsion step. Tr. 740:2-6 (Klibanov). There was no evidence presented at trial that a "low shear"

mixing step could successfully be used for step (a) to make MVLs, much less do so to yield a composition that practiced claim 7.

249. The specification does not explain how "high shear" mixing could be used in the second emulsion step to form the water-in-oil-in-water emulsion. Dr. Klibanov testified that "low shear" mixing is to be used for the second emulsion step. Tr. 744:7-10 (Klibanov). Pacira did not elicit any testimony at trial that a "high shear" mixing step could successfully be used for step (b) to make MVLs, much less do so to yield a composition that practiced claim 7.

250. The specification only provides ranges for blade diameter sizes, and does not identify the blade diameter that should be used to result in a product with the claimed stability. Tr. 123:5-9 (Hall); Tr. 578:20-23 (Yaman). The specification states that, with respect to the first emulsion step, "[i]n some further embodiments, the first mixer used in step (a) of the process is a mixer having a blade diameter of between about 8 inch to about 10 inch." JTX-4121.18. However, Pacira used an 11" diameter blade in its 200-liter process for the first emulsion step. Tr. 107:13-15 (Hall); JTX-4188.7. The specification does not describe use of an 11" diameter blade for the first emulsion step, as an 11" diameter blade is outside the range disclosed in the specification. Tr. 575:15-19 (Yaman).

251. With respect to the first emulsion step, the '495 Patent specification states that:

> Proper mixing rate is important for forming the first emulsion droplets in a proper size range, which is important to the final product yield, the MVL particle stability and release properties. It was observed that when the mixing speed is too low or too high, the droplets formed in the first emulsion were either too big or too small.

JTX-4121.13. The specification does not explain what mixing speed was considered too low or too high, nor does it explain what mixing speed should be used to yield a composition with the claimed erucic acid concentration under accelerated stability conditions. Tr. 576:24-577:3 (Yaman); Tr. 811:17-813:6 (Klibanov).

252. The specification also does not provide any testing or analysis that correlates a particular particle size with the claimed stability. Tr. 132:16-133:2 (Hall); Tr. 578:1-3 (Yaman). Notably, Pacira had internal documents that provided results for its testing, but Pacira chose not to include any of that information in the patent. JTX-4148.19, .40-41, .44-45, .48-.51.

253. The specification also does not disclose the combination of process parameters that is required to yield a compound with the required stability. Tr. 563:1-18, 571:16-572:10 (Yaman); Tr. 806:19-807:2 (Klibanov). For example, although the specification identifies certain mixer speeds, there is no disclosure of which speed should be used for a given mixer, vessel size, or blade height. Tr. 130:8-134:10 (Hall); Tr. 574:16-576:15, 576:19-577:3, 581:12-583:11 (Yaman); *compare*

JTX-4148 *with* JTX-4121. "[F]or the emulsion steps, a different blade diameter could potentially require a different mixing time speed." Tr. 120:6-9 (Hall)

254. The mixing speeds and blade diameters reported in the patent specification arose from Pacira's development of its 200-liter process. Tr. 576:16-23 (Yaman); Tr. 812:22-813:6 (Klibanov). The patent specification does not disclose what mixing speeds and blade diameters should be used for other commercial scales. Tr. 576:16-23 (Yaman).

255. The patent specification does not disclose any scientific correlation between a parameter of the manufacturing process and erucic acid concentration after storage at 25° C. Tr. 576:24-577:3 (Yaman).

5. Unpredictability of the Art

256. The prior art does not provide guidance as to what process parameters should be adjusted to yield a product with the claimed stability. Tr. 600:19-22 (Yaman).

257. Although it was known that MVLs are sensitive to process parameters like time, shear, and temperature, there was no guidance in the prior art as to how to adjust these parameters to limit the amount of degradation of DEPC to erucic acid concentration under accelerated stability conditions. Tr. 600:19-22 (Yaman).

258. Dr. Grigsby testified the "Exparel manufacturing is incredibly complex," and due to that complexity, Pacira has been unable to make batches that

practice claim 7. Tr. 179:11-14 (Grigsby). Mr. Hall testified that that are challenges in manufacturing MVLs because they are "inherently unstable during the manufacturing process." Tr. 87:21-88:5 (Hall).

259. Dr. Klibanov testified that "scaling up is far from straightforward," because "it's not nearly as simple as just using more raw materials and bigger equipment." Tr. 802:16-24 (Klibanov). Further, Dr. Klibanov testified that "processes often behave differently at different scales." *Id.* Likewise, Mr. Hall testified that Pacira's work to scale-up from 25-liter scale to 45-L scale was "quite complicated and quite complex and took a lot longer than we though it would." Tr. 94: 7-19 (Hall). Mr. Hall also testified that, in describing the second emulsion step, "the bigger the scale, the harder it is to get the job done in the same amount of time," "creating a challenging constraint for us." Tr. 111:-13 (Hall).

260. Pacira's development of its 200-liter process reinforces the unpredictability of process parameters on whether or not a composition will have the claimed stability. JTX-4188; Tr. 807:4-814:15. Pacira's current 200-liter commercial process is not the same as the process it used to manufacture its registration batches submitted to the FDA (and reported in the '495 Patent specification). Tr. 134:20-136:4 (Hall). Pacira used 450 rpm for the mixing speed for the second emulsion step for its registration batches, but adjusted the speed to 495 rpm for subsequent batches because of an out-of-specification d_{90} particle size

result. *Id.*; JTX-4148.41. Both of these speeds are described in the '495 Patent, although there is no description of the specific type of mixer, impeller diameter, and vessel geometry. Tr. 123:3-126:5 (Hall). Based on Pacira's own testing, batches made according to these different parameters had different erucic acid concentrations. Tr. 134:20-136:4 (Hall). Pacira's own manufacturing, even using the allegedly "new" process, thus yielded results within and outside the claimed accelerated erucic acid stability levels when specifically using mixing speeds disclosed in the specification of the '495 Patent. *Id.*; Tr. 436:8-441:19 (Schwendeman); Tr. 814:3-15 (Klibanov) (agreeing that "Pacira [doesn't] actually routinely get the 200 liter process to meet the erucic acid limitations of Claim 7"); JTX-4188.11.

261. It took seven years for Pacira to develop its scale-up process for manufacturing EXPAREL® from a 45-liter process, where it had considerable in-house expertise in manufacturing MVLs, reinforcing the unpredictability of the technology. Tr. 151:3-5 (Grigsby); *see* Tr. 588:6-22 (Yaman). Moreover, according to Mr. Hall, it took Pacira more than 100 development batches in order to make product at 200-liter scale that could be sold, amounting to "five years of trial-and-error." Tr. 100:2-25 (Hall).

262. In an Interrogatory response, Pacira also argued that manufacturing EXPAREL® is "very complex and involves multiple emulsion steps that must be

performed under precisely controlled conditions." Tr. 585:5-14 (Yaman). Despite all of these alleged complexities of the manufacturing process, the specification of the '495 Patent does not provide sufficient information, including the "precisely controlled conditions," to have enabled a POSA to manufacture a composition with the claimed stability. Tr. 585:15-24, 590:21-591:7 (Yaman).

6. Quantity of the Experimentation Needed

263. The quantity of experimentation needed to use the full scope of claim 7 is extensive. Tr. 590:21-591:2, 591:20-22 (Yaman). A POSA would have needed to first design the process, including determining the outputs for each unit operation that should be measured and the required parameters to manufacture a bupivacaine MVL composition at commercial scale; obtain the necessary equipment; manufacture the product; and then conduct accelerated stability testing out to six months. Tr. 585:25-590:5 (Yaman).

264. Although the general unit operations were well known in the prior art, the specific parameters of those operations that will yield a product with the required stability are not disclosed in the specification. Tr. 600:19-22 (Yaman). Because the specification provides no analysis as to the required process conditions to yield a product that practices the claim, a POSA would have needed to conduct extensive experiments for each unit operation involved in the process. Tr. 585:25-590:5 (Yaman). For example, POSA would have been needed to conductive extensive

experiments at commercial scale to evaluate the impact of each of the process parameters to attempt to yield a composition with the required attributes. *Id*. This is a matter of trial-and-error, and is not routine to conduct such experimentation at commercial scale. Tr. 589:14-20 (Yaman).

265. Claim 7 is directed to a composition prepared by a process at "commercial scale"; therefore, any such experimentation would have needed to be performed at "commercial scale," which is more costly and burdensome than a laboratory scale or bench-scale experiment. Tr. 589:10-23 (Yaman); JTX-4121.21 (23:29-32).

266. Claims 7 is directed to a composition with certain erucic acid concentration after one and six months of storage under accelerated stability conditions. JTX-4121.21 (23:29-32). To evaluate whether a composition had the required stability would have necessarily required waiting six months under accelerated stability conditions, plus additional time to obtain results from testing the product for erucic acid concentration. Tr. 130:8-131:5 (Hall); Tr. 587:7-17 (Yaman). This further compounds the undue experimentation that would have been required as a POSA would have had to wait more than six months until results were available to determine whether or not the composition had the required stability. Tr. 130:8-131:5 (Hall); Tr. 587:7-17 (Yaman). If the composition did not, the process

would need to be modified; additional batches manufactured; and then accelerated stability conducted on the new batches. Tr. 587:18-589:9 (Yaman).

267. Even if a POSA were able to make a composition that practiced claim 7 using the mixing speeds and blade diameters disclosed in the patent specification, those parameters would not work for a different commercial scale and therefore further experimentation would need to be performed to make a composition at other commercial scales. Tr. 589:24-590:5 (Yaman). As claim 7 is not limited to a composition prepared by a 200-liter scale process, a POSA would have to conduct extensive experimentation through trial and error at each desired commercial scale in order to yield a composition that would practice claim 7. *Id.*

268. Pacira's development of a 200-liter process reinforces the undue experimentation required to prepare a composition that would practice claim 7. Tr. 590:6-591:2 (Yaman). Over a period of seven years, Pacira engineers performed process development on each discrete unit operation sequentially; once each operation had demonstrated satisfactory performance, development was advanced to the next unit operation; then they conducted further testing to evaluate the impact of various parameters on the final product quality; and then conducted yet further testing to determine the allowable ranges that would yield the claimed quality. Tr. 130:8-134:10 (Hall); JTX-4148.16, 38, 41.

269. The Pacira engineers also encountered problems that led to failed batches, including crystallization of bupivacaine that they purportedly solved by modifying the mechanical design of the sparging elements used in the solvent removal steps (details of which are also not disclosed in the patent specification). Tr. 133:3-13 (Hall); JTX-4148.41. Furthermore, recognizing that their product had a particle size diameter that was out of specification, the Pacira engineers modified the mixer speed for the second emulsion step, manufactured new batches using the new speed, and then conducted accelerated stability testing on the new batches—only to discover that the new batches did not have the claimed stability. Tr. 134:20-136:4, 139:10-144:7 (Hall); Tr. 436:9-441:19 (Schwendeman); JTX-4188.11; JTX-4053.3; DTX-2551.1; DTX-2552.1; DTX-2553.1.

270. Dr. Klibanov agreed that a "substantial amount" of experimentation would be required to practice claim 7. Tr. 751:3-11 (Klibanov). Dr. Klibanov's testimony—that it would be "routine experimentation" to start with information disclosed in the patent specification for a 200-liter process to arrive at a composition that practiced claim 7 at a 400-liter scale (Tr. 813:3-814:15 (Klibanov))—is contrary to Pacira's own development experience. Pacira conducted extensive experimentation to determine process parameters that would a yield an MVL product at 200-liter scale, and yet still is not able to routinely make a product that practices claim 7. Tr. 139:10-144:7 (Hall); Tr. 178:24-179:25 (Grisby); Tr. 462:16-20

(Schwendeman (explaining that, for "all the 200-liter data, there is a very large range . . . some are 92 to 133" µg/mL of erucic acid after six months at 25 C)); Tr. 814:5-15 (Klibanov (agreeing that "Pacira [doesn't] actually routinely get the 200-liter process to meet the erucic acid limitations of Claim 7")); DTX-2551.1; DTX-2552.1; DTX-2553.1; DTX-3114.1. Moreover, Dr. Grigsby testified that despite wanting each batch to have less than 99 µg/mL of erucic acid after six months at 25° C, Pacira has been unable to achieve that because "EXPAREL manufacturing is incredibly complex." Tr. 179:11-14 (Grigsby).

271. Dr. Zhang from Jiangsu Hengrui testified at trial that he relied in part on the prior art '838 patent in designing the process to manufacture the ANDA Products. JTX-4293.5-6 (Zhang Tr. 186:11-12, 186:13-17, 187:23-24, 187:25-188:17, 188:20-189:4, 189:10, 189:14-21, 189:24). But there is no evidence that batches of the ANDA Products actually practice the limitations of claim 7. Tr. at 294:2-22, 310:15-25 (Karaborni).

III. UNENFORCEABILITY DUE TO INEQUITABLE CONDUCT

A. RELEVANT PRACTICES AND PROCEDURES DURING PROSECUTION

1. Duty of Candor

272. During prosecution, examiners are trained to use to USPTO databases for finding prior art, which include public information such as patent, patent applications, and journal articles. Tr. 619:20-620:13 (Slifer). In addition, USPTO

examiners expect to receive information on the prior art through applicant disclosures, as set forth in the Manual of Patent Examination Procedure ("MPEP"). Tr. 620:14-19 (Slifer).

273. Section 2001 of the MPEP instructs applicants that "[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." Tr. 620:23-621:17 (Slifer); Tr. 844:11-17 (Godici); DTX-2200.2. The duty of candor encompasses a duty to be honest, complete, and truthful in statements to the USPTO. Tr. 621:18-622:1 (Slifer); Tr. 844:23-845:3, 846:23-848:3 (Godici). The duty of good faith also requires that applicants conduct themselves so as not to deceive the USPTO, including correcting errors and not taking advantage of misunderstandings. Tr. 621:18-622:1 (Slifer); Tr. 844:23-845:3, 846:23-848:3 (Godici). This duty is further reflected in 37 CFR § 11.18, which states that by filing a paper with the USPTO, the person filing the paper is certifying that the statements made in that document are truthful based on a reasonable inquiry. Tr. 625:24-626:15 (Slifer); DTX-2562.1.

274. The duty of candor prohibits intentionally making misleading statements during prosecution, and making such statements may rise to the level of egregious prosecution misconduct. Tr. 846:23-847:1, 847:11-17 (Godici). The duty

of candor and good faith prohibits intentional mischaracterizations of the prior art, even if the underlying reference was provided to the examiner. Tr. 847:18-21, 847:22-848:3 (Godici) ("[Y]ou can't intentionally try to pull the wool over the patent examiner's eyes by making some false statement about the prior art, even if the prior art was before the examiner.").

275. The duty of candor and good faith is a fundamental principle underlying the operation of the patent system and is "fundamental to the process at the patent office." Tr. 843:25-844:4 (Godici). Patent examiners at all levels of seniority operate on the assumption that applicants will comply with their duty of candor and good faith. Tr. 844:5-10 (Godici).

276. One purpose for the duty of candor is that examiners have a limited amount of time for searches and examination of patents, and do not have the time, training, or skills to independently evaluate the truthfulness of applicant statements. Tr. 622:12-21 (Slifer). The duty of candor and good faith puts the burden on the applicants, so that the examiners can rely on the information presented to them. *Id.*

277. The definition of "material information" during prosecution is broader than the "but-for materiality" standard used during litigation to assess inequitable conduct. Tr. 622:22-623:23 (Slifer). During prosecution, information is material if it would help the examiner make a decision as to whether the claims before him are allowable. *Id.*

278. Section 2004 of the MPEP sets forth best practices for applicants to ensure that they appropriately disclose material information. Tr. 623:24-624:12 (Slifer); DTX-2200.10. During prosecution, summarizing material information in an incomplete manner does not comply with the duty to disclose material information, because it risks misleading the examiner. Tr. 624:13-625:8 (Slifer); DTX-2200.11 ("[C]are should be taken to see that the prior art or other information cited in a specification . . . . is not incompletely characterized.").

279. If there is any doubt as to whether information is material, the MPEP instructs applicants that the information should be disclosed to the examiner, so that the examiner can evaluate that information and make an independent decision. Tr. 625:9-19 (Slifer); DTX-2200.12.

280. The duty of candor also requires that applicants ensure that their statements to the USPTO and the FDA are consistent, and that material information is not provided to the FDA but withheld from the USPTO.

281. For example, in 2022, the USPTO issued a Federal Register notice clarifying applicants' duty to disclose material information related to submissions to other federal agencies such as the FDA. Tr. 629:16-631:7 (Slifer); DTX-3095.1-2. This clarification was precipitated by concerns from the White House and certain Senators that inconsistent statements were being made to the USPTO to obtain

patents, as compared to statements made to the FDA to secure approval of pharmaceutical products. Tr. 629:16-631:7 (Slifer); DTX-3095.1-2.

282. In response to these concerns, the USPTO issued guidance reconfirming that applicants' duty of disclosure and reasonable inquiry required applicants to ensure that statements made to the USPTO and other government agencies were consistent with each other. Tr. 631:8-632:23 (Slifer); DTX-3095.2-3; DTX-3104.21. The USPTO also stated that providing material information to other government agencies, including the FDA, while simultaneously withholding the same information from the USPTO, undermined both the intent and spirit of the duty of disclosure and violated those duties. Tr. 631:8-632:23 (Slifer); DTX-3095.2-3; DTX-3104.21. Guidance on this point was added to Section 2015 of the MPEP. Tr. 631:8-632:23 (Slifer); DTX-3095.2-3; DTX-3104.21. The FDA's 2022 confirmation of the duty of candor as applied to FDA submissions was not a policy change; it was based on long-standing CFR provisions requiring these ethical duties of applicants. Tr. 632:24-633:3 (Slifer).

283. The duty of candor was particularly important for the '495 Patent, in view of its product-by-process claims. Section 2113 of the MPEP instructs applicants that as a practical matter, the USPTO does not have the ability to manufacture or purchase prior-art products to assess the patentability of product-by-process claims. Tr. 626:18-628:11 (Slifer); DTX-3106.143. As such, the examiner

is particularly reliant on applicants to disclose material information regarding prior art products in the context of product-by-process claims, such as those in the '495 Patent. Tr. 626:18-628:11 (Slifer); DTX-3106.143.

284. The duty of candor was also particularly important for the '495 Patent because it was an accelerated application. During prosecution, Pacira filed a request for prioritized examination of the application for the '495 Patent. Tr. 633:17-634:6 (Slifer); JTX-4001.2. Prioritized examination would allow examination to be complete within twelve (12) months, rather than anywhere from eighteen (18) months to two (2) or three (3) years for a typical application. Tr. 633:17-634:6 (Slifer). Because of the accelerated timeline for prioritized examination, collaborative communications and the duty of candor are even more important in that context than for a typical application. Tr. 634:7-15 (Slifer).

2. Examination of Product-by-Process Claims

285. Section 2113 of the MPEP instructs applicants that for product-by-process claims, once the examiner provides a *prima facie* case of obviousness, the burden shifts from the USPTO to the applicant to come forward with evidence that the claimed product is not obvious over prior art products. Tr. 628:12-629:1 (Slifer); DTX-3106.142. For other categories of claims, the examiner would have the burden to establish that the claims were unpatentable, rather than merely setting forth a *prima facie* case. Tr. 628:12-629:1 (Slifer); DTX-3106.142.

286. Patent examiners are trained that "a *prima facie* case of obviousness exists where the claimed ranges or amounts do not overlap with the prior art but are merely close," where "one skilled in the art would expect them to have the same properties." DTX-3106.307 (MPEP Ch. 2100) (citation omitted).

3. Declarations in Support of Patentability

287. Examiners are taught to evaluate declarations for whether they are responsive to the issue of concern and whether they facially set forth sufficient facts in support. Examiners do not independently investigate whether the statements in an inventor declaration are factually accurate. Tr. 646:22-647:12 (Slifer).

288. Section 716 of the MPEP sets forth the rules for affidavits and declarations under 37 CFR § 1.132, traversing rejections from the USPTO. Tr. 862:3-19 (Godici); DTX-3099.241 (MPEP Ch. 700). The MPEP instructs examiners and applicants that declarations under 37 CFR § 1.132 may overcome an obviousness rejection by presenting evidence that the claimed invention is superior in a property that is shared with the prior art, but that in order to overcome a rejection on this basis, the applicant must present differences and results that are "in fact unexpected and unobvious and of both statistical and practical significance." Tr. 863:5-864:12 (Godici); DTX-3099.247-48 (MPEP Ch. 700).

4. Broadest Reasonable Interpretation

289. During prosecution, examiners are trained to examine claims under the broadest reasonable interpretation, informed by what would be reasonable from the perspective of a POSA (as set forth in § 2111 of the MPEP). Tr. 853:9-854:9 (Godici); DTX-3106.122 (MPEP § 2111). Examiners are further trained that when interpreting claims, it is improper to import claim limitations from the specification if those limitations do not appear in the language of the claims. Tr. 854:10-21 (Godici); DTX-3106.123 (MPEP § 2111).

290. The named inventors consistently testified that in their view, the only new physical property of the composition in claim 1 was the erucic acid concentration at the one-month timepoint. Tr. 183:2-185:25 (Grigsby); JTX-4287.6-7 (Ardekani Tr. 78:1-19, 80:13-16, 80:18); JTX-4289.15 (Los Tr. 79:13-14, 79:20-80:5, 80:9-11); *see also* JTX-4289.10 (Los Tr. 61:3-5, 61:7-11, 61:14) (Pacira's 45-liter manufacturing process was a "commercial scale" process).

291. For purposes of determining but-for materiality during prosecution, the broadest reasonable interpretation of the claims does not include any structural or functional features other than the explicitly claimed features of (1) the erucic acid concentration at the one-month timepoint and (2) the claimed concentration of bupivacaine.

B. UNDISCLOSED DATA IN THE POSSESSION OF INVENTORS AND PROSECUTION COUNSEL

292. During prosecution, Pacira's inventors and prosecution counsel were in possession of significant amounts of internal data relevant to the pending claims—specifically, the data gathered and analyzed by the inventors and prosecution counsel in connection with prosecution of the '495 Patent. *Infra* Section III.C.1.a-b.

293. In the specification of the '495 Patent, Pacira disclosed only limited data on erucic acid in 45-liter batches of EXPAREL®. Specifically, Pacira disclosed only average values for erucic acid at the two-, three-, and six-month timepoint for seven 45-liter "reference samples," and indicated that no data existed at the one-month timepoint for those batches. JTX-4121.19 (20:49-67); JTX-4289:16-17 (Los Tr. 81:10-81:22, 81:24-82:5, 82:7-14, 82:22-83:5, 85:5-7); *infra* Section III.C.2.a.(1). While Pacira disclosed individual batch values for the 200-liter batches (batches 1, 2, and 3 in the specification), it did not disclose individual batch results for the 45-liter reference samples, or data from any of the additional 45-liter batches for which the inventors had Pacira's internal data. JTX-4121.19 (20:49-67); JTX-4289:16-17 (Los Tr. 81:10-81:22, 81:24-82:5, 82:7-14, 82:22-83:5, 85:5-7); *infra* Section III.C.2.a.(1).

294. Pacira did not disclose any data on 45-liter EXPAREL to the USPTO other than what appears on the face of the '495 Patent. Tr. 636:18-21 (Slifer); JTX-

4288.20-21 (Dai Tr. 162:6-16, 162:24-163:2, 163:5-167:10); JTX-4289.43 (Los Tr. 197:25-198:3, 198:9).

1. Los Spreadsheet

295. Ms. Los prepared the compilation of data that served as the basis for the data in the '495 Patent in an Excel spreadsheet ("the Los Spreadsheet"). JTX-4289.18, 27 (Los Tr. 91:13-16, 131:14-18).

296. On January 22, 2021—the same day the application leading to the '495 Patent was filed—Ms. Los sent an "updated version of the spreadsheet" with the data underlying the '495 Patent to Dr. Dai, Mr. Molloy, and Dr. Grigsby, as well as one of Jane Dai's associate attorneys (Daniel Kamkar). JTX-4119.1; JTX-4037.18-19; JTX-4288.9-10 (Dai Tr. 110:17-111:02, 112:5-7, 112:12-14); JTX-4289.18-19 (Los Tr. 96:9-25); JTX-4119.1.

297. The data in the Los Spreadsheet was the basis for the data tables in the '495 Patent. JTX-4288.10 (Dai Tr. 114:06-8, 114:15-21, 114:25-115:03); JTX-4037. Specifically, the erucic acid concentration data on page 18 of the Los Spreadsheet is the data underlying Table 1A of the '495 Patent. JTX-4288.11 (Dai Tr. 118:07-11, 118:12-21); JTX-4037.18; JTX-4289.27 (Los Tr. 131:14-18).

298. The Los Spreadsheet contained erucic acid concentration data on Pacira's three 200-liter registration batches of EXPAREL®: 129855, 129856, and

129860. JTX-4289.20-21 (Los Tr. 118:13-119:17, 119:18-24, 120:2-23); JTX-4037.18.

299. The Los Spreadsheet also contained stability data on erucic acid concentration and external pH for ten 45-liter batches of EXPAREL® manufactured at Pacira's Science Center Campus ("SCC") commercial manufacturing facility in San Diego: lots 16-P004, 16-3088, 16-3089, 16-3090, 17-3142, 17-4135, 17-4136, 20-3066, 20-3067, and 20-4076. JTX-4037.18-19; JTX-4289.20 (Los Tr. 118:13-119:17). It did not contain data for any 45-liter batches manufactured at Pacira's Swindon facility, despite the fact that Pacira also manufactured 45-liter batches at the Swindon facility prior to 2021. JTX-4037.18-19; JTX-4289.20 (Los Tr. 118:13-119:17); Tr. 349:12-350:5 (Molloy).

300. Only seven of these batches were actually used to calculate the values in Table 1A—the bottom seven batches on page 18 of the Los Spreadsheet. JTX-4288.11 (Dai Tr. 119:15-24); JTX-4037.18; JTX-4289.22-23 (Los Tr. 122:16-22, 124:2-12).

301. The Los Spreadsheet does not indicate which of the 200-liter or 45-liter batches were commercially sold, or intended for commercial distribution. JTX-4037.18; JTX-4289.23 -24 (Los Tr. 124.25-125:18); Tr. 424:8-11 (Schwendeman). The 200-liter batches in the Los Spreadsheet (129855, 129856, and 129860) were not commercially distributed; rather, they were registration batches whose data was

submitted in support of Pacira's FDA filing seeking approval of the 200-liter process. JTX-4037.18; JTX-4289.20-21 (Los Tr. 119:18-24, 120:2-23); JTX-4053.3. Of the 45-liter batches in the Los Spreadsheet, lots 16-3088, 16-3089, 16-3090 were commercially sold; the other seven batches were not commercially sold. JTX-4037.18; Tr. 423:25-424:7 (Schwendeman); DTX-3109.32. Nonetheless, the '495 Patent represents that the data from the Los Spreadsheet (i.e., the from "reference samples" in Table 1A) reflects the properties of the prior art "commercial Exparel® product." JTX-4121.16 (13:49-51); JTX-4288.6-8 (Dai Tr. 88:09-10, 88:11-12, 88:16, 88:23-89:12, 89:15-16, 89:17-19, 89:22-23, 93:1-7, 93:10); JTX-4289.13-14 (Los Tr. 74:18-75:5, 75:8, 76:14-17, 76:19).

302. None of the individual batch data for 45-liter EXPAREL® in the Los Spreadsheet was disclosed to the USPTO in the specification of the '495 Patent, or during prosecution of the '495 Patent. Tr. 637:18-21 (Slifer); JTX-4288.20-21 (Dai Tr. 162:6-16, 162:24-163:2, 163:5-167:10); JTX-4289.43 (Los Tr. 197:25-198:3, 198:9).

2. Ardekani Data

303. The erucic acid concentration data in the Los Spreadsheet was compiled from a larger collection of data, the Ardekani Data. Tr. 765:8-11 (Klibanov) (agreeing that the Ardekani Data is a basis for the Los Spreadsheet).

304. In its Interrogatory responses, Pacira stated that the stability data for the 45-liter batches was "chosen because the 25° C stability study data at 1 month, 2 month, 3 month, and 6 month time points for these batches had been collected for a different study called the prefilled syringe stability study, and it was convenient to use the same lots." DTX-2176.29. Ms. Los confirmed at deposition that it was "convenient" for her and Dr. Ardekani to use the same lots for the Los Spreadsheet as had been collected for the prefilled syringe compatibility study. JTX-4289.36 (Los Tr. 163:24-164:6, 164:8).

305. Dr. Ardekani confirmed that he was in charge of the prefilled syringe study, and that he reviewed "the same documents from QC" for the prefilled syringe study regarding 45-liter stability data as he did in connection with the '495 Patent. JTX-4287.12-13 (Ardekani Tr. 135:20-21, 135:23-136:2, 137:4-6, 137:8-10, 137:15-16).

306. The 45-liter stability data for the prefilled syringe study was "requested . . . from [Pacira's] regulatory group" in early December of 2020. JTX-4289.35-36 (Los Tr. 161:21-161:22, 161:25-162:5, 162:7-11, 165:16-20). Specifically, on December 7, 2020, Dr. Ardekani emailed Tricia Glenn (the head of Pacira's Quality Control group) requesting stability data at 5° C and 25° C for the prefilled syringe study. JTX-4287.13-14 (Ardekani Tr. 138:21-139:25, 140:9-17, 140:19-22); DTX-2465.1-2. On December 9, 2020, Dr. Ardekani received an email

containing a set of stability data (the "Ardekani Data"), which he forwarded on the same day to Ms. Los and two other named inventors (Louie Garcia and Paige Davis). JTX-4287.15, 22 (Ardekani Tr. 142:4-16, 142:18, 142:19-143:8, 143:10-12).

307. The Ardekani Data included the 45-liter stability data for the ten SCC lots in the Los Spreadsheet. DTX-2465.42 (Lot 20-6067), 44 (Lot 16-3088), 45 (Lot 20-3066), 47 (Lot 20-4076), 50 (Lot 16-3089), 52 (Lot 16-3090), 57 (Lot 16-P004), 59 (Lot 17-3142), 65 (Lot 17-4135), 67 (Lot 17-4136); Tr. 766:13-19 (Klibanov); JTX-4037.18. However, the Ardekani Data also contained stability data for additional lots of EXPAREL®, including eight 45-liter lots of EXPAREL manufactured at Pacira's Swindon facility. JTX-4287.15-16 (Ardekani Tr. 146:4-20, 146:23-24); DTX-2465.3. The stability data for the eight 45-L Swindon batches indicated that each of those batches met the one, two, three, and six-month erucic acid concentration limitations of claims 1, 3, 5, and 7 of the '495 Patent. JTX-4287.16-19 (Ardekani Tr. 147:22-148:12, 148:15-16, 148:22-23, 148:25-149:3, 149:5-8, 149:11-14, 149:19-20, 149:21-24, 150:23-151:4, 151:6-16, 151:17-23, 152:1-6, 152:8, 152:13-14, 152:16-153:3, 153:7-8, 153:19-22, 154:2, 154:11-12, 154:13, 154:20-22, 154:24); Tr. 431:4-9, 431:25-435:3 (Schwendeman); DTX-2465.3, 5, 7, 9, 11, 13, 15, 17, 19. None of the Swindon lots in the Ardekani Data were included in the Los Spreadsheet. Tr. 435:4-8 (Schwendeman).

308. For each of the batches in the Ardekani Data with data at 25 °C, the Ardekani Data also contained stability data at 5° C. DTX-2465.4-17, 41-52, 56-59, 62-67, 69-70, 72-73, 75-78, 80-81, 83-84; Tr. 767:4-768:18 (Klibanov).

C. PROSECUTION MISCONDUCT

1. Pacira Concealed But-For Material Data on Batches of Prior-Art EXPAREL®

309. During prosecution of the '495 Patent, the applicants were in possession of data for individual batches of 45-liter EXPAREL® as included in the Los Spreadsheet and Ardekani Data, including data on erucic acid concentration at the one-, two-, three-, and six-month time point during storage at 25 °C. *Supra* Section III.B. This data was never disclosed to the USPTO during prosecution. *Id.* As discussed below, this withheld data would have been but-for material to the issuance of one or more claims of the '495 Patent.

a. The Withheld Data in the Los Spreadsheet Was But-For Material

310. The withheld data in the Los Spreadsheet included erucic acid concentration data for batches 16-P004, 16-3088, 16-3089, and 16-3090 after storage at 25 °C for one, two, three, and six months. JTX-4037.18; Tr. 423:25-424:7, 425:18-426:2 (Schwendeman); Tr. 351:10-353:9 (Molloy); Tr. 765:12-768:18 (Klibanov); JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7); JTX-4289.24 (Los Tr. 125:19-126:2).

311. Batch 16-P004 had an erucic acid concentration of less than 20 µg/mL after one month at 25 °C; 36 µg/mL after two months; and 51 µg/mL after three months. Tr. 423:25-424:7, 425:18-426:2 (Schwendeman); Tr. 351:10-353:9 (Molloy); Tr. 765:12-768:18 (Klibanov); JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7); JTX-4289.24 (Los Tr. 125:19-126:2).

312. Batch 16-3088 had an erucic acid concentration of 25 µg/mL after one month at 25 °C; 35 µg/mL after two months; and 53 µg/mL after three months. Tr. 423:25-424:7, 425:18-426:2 (Schwendeman); Tr. 351:10-353:9 (Molloy); Tr. 765:12-768:18 (Klibanov); JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7); JTX-4289.24 (Los Tr. 125:19-126:2).

313. Batch 16-3089 had an erucic acid concentration of less than 20 µg/mL after one month at 25 °C; 34 µg/mL after two months; and 54 µg/mL after three months. Tr. 423:25-424:7, 425:18-426:2 (Schwendeman); Tr. 351:10-353:9 (Molloy); Tr. 765:12-768:18 (Klibanov); JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7); JTX-4289.24 (Los Tr. 125:19-126:2).

314. Batch 16-3090 had an erucic acid concentration of less than 20 µg/mL after one month at 25 °C; 36 µg/mL after two months; and 54 µg/mL after three months. Tr. 423:25-424:7, 425:18-426:2 (Schwendeman); Tr. 351:10-353:9 (Molloy); Tr. 765:12-768:18 (Klibanov); JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7); JTX-4289.24 (Los Tr. 125:19-126:2).

315. Batches 16-3088, 16-3089, and 16-3090 were all commercially sold, and all four batches met every limitation of claims 1, 3, and 5 of the '495 Patent. Tr. 422:14-24, 423:25-424:7, 424:12-426:8 (Schwendeman); DTX-3111.1; Tr. 765:12-25 (Klibanov). The sale of each of these batches therefore anticipated at least claims 1, 3, and 5 of the '495 Patent. *Supra* Section II.A.1-3. Although batch 16-P004 was not itself commercially sold, it was manufactured at one of Pacira's commercial facilities using Pacira's commercial manufacturing process, and a POSA would have expected the stability data for 16-P004 to reflect the stability properties of some of Pacira's commercially sold prior art batches of 45-liter EXPAREL®. *Supra* Sections II.A-B.

316. Pacira repeatedly relied on the one-month erucic acid concentration and representations of "improved stability" as a purported point of novelty during prosecution, and the Examiner explicitly relied on the purported novelty of the erucic acid limitation (the "claimed storage stability") as one of his reasons for allowance. JTX-4001.2311; *supra* Section C.2.

317. The withheld erucic acid data in the Los Spreadsheet showed that these batches met the limitations of at least claims 1, 3, and 5 of the '495 Patent, and that those claims were anticipated by prior art EXPAREL®. If the Examiner had been aware that claims 1, 3, and 5 were anticipated, he would not have allowed the claims

to issue. The withheld erucic acid data in the Los Spreadsheet was therefore but-for material.

318. Dr. Klibanov's only argument as to why claims 1, 3, and 5 were not anticipated by the sale of batches 16-3088, 16-3089, or 16-3090 was that the batches did not meet the "prepared by a commercial scale process" limitation, which he interpreted to require (1) a process practiced on a scale larger than 45-liter, and (2) "new structural features" including "lower lipid hydrolysis, higher internal lysine and dextrose concentrations, more desirable internal pH . . . and finally, improved MVL particle strength during product transportation." Tr. 700:16-701:16, 703:25-704:12, 752:7-753:2 (Klibanov). Dr. Klibanov did not identify any other limitation of claims 1, 3, and 5 as a basis why the claims were not anticipated by the sale of these three batches of prior art EXPAREL®.

319. As discussed above, Dr. Klibanov's interpretation of the Court's claim construction is incorrect, and these claims were therefore anticipated. *Supra* Section II.A.1.e.

320. Additionally, during prosecution, the Examiner would have applied the broadest reasonable interpretation of the claims, which would not include Dr. Klibanov's additional "structural features." *Supra* Section III.A.4. This is corroborated by the fact that Pacira made arguments to the USPTO purportedly distinguishing its claimed product from the prior art based on "erucic acid levels

over a period of six months," not any of the other purported "structural/functional features" discussed by Dr. Klibanov. Tr. 838:25-840:10 (Godici); JTX-4001.2176, .2179.

321. As discussed in further detail below, the anticipatory data in the Los Spreadsheet was in the possession of prosecution counsel Jane Dai and named inventor Kathleen Los. *Supra* Section III.B, *infra* Section III.D.2.a.(2). Dr. Dai and Ms. Los reviewed and analyzed this data during prosecution—indeed, the data in the Los Spreadsheet was the basis for the data in the specification of the '495 Patent. *Supra* ¶ 298. However, Dr. Dai and Ms. Los never disclosed the individual batch data for the 45-liter batches in the Los Spreadsheet to the USPTO during prosecution. *Supra* ¶ 294. Instead, they affirmatively concealed the existence of the one-month data by reporting in Table 1A that one-month data for the reference batches did not exist in Table 1A. *Infra* Section III.C.2.

b. The Withheld Data in the Ardekani Data Was But-For Material

322. The Ardekani Data contained data for erucic acid after storage at 25 °C for one, two, three, and six months for eight 45-liter lots of EXPAREL® from Pacira's Swindon manufacturing facility: lots 037188, 037189, 037190, 037191, 037192, 037193, 047903, and 126837. DTX-2465.3, .5, .7, .9, .11, .13, .15, .17, .19.

323. Lot 037188 had an erucic acid concentration of 23 µg/mL after one month at 25 °C; 35 µg/mL after two months; 46 µg/mL after three months; and 90 µg/mL after six months. DTX-2465.5.

324. Lot 037189 had an erucic acid concentration of 25 µg/mL after one month at 25 °C; 35 µg/mL after two months; 46 µg/mL after three months; and 89 µg/mL after six months. DTX-2465.7.

325. Lot 037190 had an erucic acid concentration of less than 20 µg/mL after one month at 25 °C; 33 µg/mL after two months; 45 µg/mL after three months; and 83 µg/mL after six months. DTX-2465.9.

326. Lot 037191 had an erucic acid concentration of "non-detected" after one month at 25 °C; 35 µg/mL after two months; 44 µg/mL after three months; and 80 µg/mL after six months. DTX-2465.11.

327. Lot 037192 had an erucic acid concentration of "non-detected" after one month at 25 °C; 35 µg/mL after two months; 43 µg/mL after three months; and 80 µg/mL after six months. DTX-2465.13.

328. Lot 037193 had an erucic acid concentration of "non-detected" after one month at 25 °C; 35 µg/mL after two months; 42 µg/mL after three months; and 78 µg/mL after six months. DTX-2465.15.

329. Lot 047903 had an erucic acid concentration of 25 µg/mL after one month at 25 °C; 34 µg/mL after two months; 43 µg/mL after three months; and 79 µg/mL after six months. DTX-2465.17.

330. Lot 126837 had an erucic acid concentration of less than 20 µg/mL after one month at 25 °C; 35 µg/mL after two months; 41 µg/mL after three months; and 102 µg/mL after six months. DTX-2465.19.

331. The stability data for the eight 45-L Swindon lots indicated that each of those batches met the one-, two-, three-, and six-month limitations of claims 1, 3, 5, and 7 of the '495 patent. JTX-4287.16-19 (Ardekani Tr. 147:22-148:12, 148:15-16, 148:22-23, 148:25-149:3, 149:5-8, 149:11-14, 149:19-20, 149:21-24, 150:23-151:4, 151:6-16, 151:17-23, 152:1-6, 152:8, 152:13-14, 152:16-153:3, 153:7-8, 153:19-22, 154:2, 154:11-12, 154:13, 154:20-22, 154:24); Tr. 431:4-9, 431:25-435:3 (Schwendeman); DTX-2465.3, .5, .7, .9, .11, .13, .15, .17, .19.

332. As discussed in more detail below, all of the data on these 45-liter batches of EXPAREL® within the Ardekani Data was in Ms. Los's possession prior to the filing of the '495 Patent. *Infra* Section III.D.2.b. The Ardekani Data was the basis for the Los Spreadsheet, and Ms. Los received all of the Ardekani Data in December 2020, shortly before filing the '495 Patent. *Id.* However, the Ardekani Data was not included in the Los Spreadsheet (based on the unredacted portions of

the document produced in this case), and data on these eight batches was never provided to the USPTO during prosecution. JTX-4037.18; *supra* Section III.B.2.

333. Although none of these eight batches in the Ardekani Data were themselves sold commercially, they were manufactured in Pacira's commercial facility, using Pacira's commercial process, and would have been expected to reflect the properties of at least some of Pacira's commercially sold prior art lots of EXPAREL®. *See supra* Section II.A.4. The results of stability testing at 25 °C for 45-liter batches of EXPAREL® would have been expected to reflect the properties of Pacira's commercial batches of 45-liter EXPAREL®, whether or not the batches tested for stability were themselves commercially sold. *Id.* This is corroborated by the fact that the '495 Patent itself relied interchangeably on data for sold and unsold batches of 45-liter EXPAREL® as evidence of the properties of "the commercial Exparel® product." JTX-4121.16 (13:49-55); JTX-4288.6-8 (Dai Tr. 88:09-10, 88:11-12, 88:16, 88:23-89:12, 89:15-16, 89:17-19, 89:22-23, 93:1-7, 93:10); JTX-4289.13-14 (Los Tr. 74:18-75:5, 75:8, 76:14-17, 76:19).

334. Pacira repeatedly relied on the one-month erucic acid concentration and representations of "improved stability" as a purported point of novelty during prosecution, and the Examiner explicitly relied on the purported novelty of the erucic acid limitation (the "claimed storage stability") as one of his reasons for allowance. JTX-4001.2311; *supra* Section I.C.2. At trial, Pacira admitted that there was no

meaningful difference in erucic acid concentrations at the one-, two-, or three-month timepoints (Tr. 169:25-170:12 (Grigsby)); rather, Pacira relied heavily on the six-month erucic acid concentration of erucic acid as a purported point of novelty for Claim 7. *See, e.g.*, Tr. 704:25-705:16 (Klibanov).

335. The withheld portions of the Ardekani Data would have indicated to the Examiner that the claimed erucic acid levels were not novel at ***any*** of the claimed timepoints (including the six-month timepoint). As discussed above, every batch of 45-liter EXPAREL® met all other limitations of claims 1, 3, 5, and 7 of the '495 Patent, including these eight batches. *Supra* Section II.A.1. The withheld portions of the Ardekani Data indicated that at least claims 1, 3, 5, and 7 were anticipated by prior art EXPAREL®. If the Examiner had been aware that claims 1, 3, 5, and 7 were anticipated, he would not have allowed the claims to issue. As such, the withheld portions of the Ardekani Data were but-for material.

336. As discussed in further detail below, the anticipatory data for the 45-liter Swindon batches in the Ardekani Data was in the possession of named inventor Kathleen Los. *Infra* Section III.D.2.b. Ms. Los reviewed and analyzed this data during prosecution—indeed, the Ardekani Data was the basis for the data in the Los Spreadsheet. *Supra* Section III.B. However, Ms. Los did not include the Ardekani Data in the Los Spreadsheet, and never disclosed the individual batch data for the 45-liter Swindon batches in the Ardekani Data to the USPTO during prosecution.

Supra Section III.B.2. Instead, she affirmatively misrepresented the properties of prior art 45-liter EXPAREL® by telling the USPTO that the 200-liter product had "improved stability," the falsity of which would have been revealed by the undisclosed data in her possession. *Supra* Section 1.C.2.

c. The Withheld Stability Data Was Not "Cumulative" of Figure 3B

337. Pacira has argued that the withheld one-month stability data was "cumulative" of an extrapolated one-month average for the reference samples purportedly disclosed in Figure 3B of the specification, and Pacira's withholding of stability data from the USPTO therefore was not but-for material. *See, e.g.*, Tr. 41:19-43:3 (Pacira Opening Statement); D.I. 298 Tab 9 (Plaintiffs' Contested Facts) at 92. For many reasons, this argument is inaccurate.

338. **First**, the withheld one-month stability data was not "cumulative" based on Figure 3B because Figure 3B would not have adequately conveyed to the USPTO or a POSA that some prior art batches of 45-liter EXPAREL® had an erucic acid concentration of "less than about 23 μg/mL" after one month of storage at 25 °C. Tr. 427:12-429:14 (Schwendeman).

339. Consistent with the lack of one-month data in Table 1A, Figure 3B does not present data at the one-month time point for Batches 1, 2, and 3 (i.e., the 200-liter samples) or for the "reference samples" (i.e., the 45-liter samples)—the measured data points are represented by triangles and circles, and there are no

triangles or circles at the one-month timepoint. Tr. 173:20-23 (Grigsby); JTX-4288.26 (Dai Tr. 251:20-252:2); JTX-4121.8; Tr. 427:11-428:6, 428:12-16 (Schwendeman); Tr. 774:7-13 (Klibanov). A POSA reading Figure 3B would not have understood that Pacira was in possession of data at the one-month timepoint for its 45-liter reference samples, much less that Pacira's data showed anticipation of the one-month erucic acid limitation. Tr. 427:11-428:6, 428:12-16 (Schwendeman).

340. A POSA or USPTO examiner would not know how to interpret the unlabeled extension of the dotted line in Figure 3B to approximately the one-month timepoint. Figure 3B does not use the typical graph format for linear regression, which would be to extend the line above and below the actual data points reported. Tr. 428:7-11 (Schwendeman). It also does not include the one-month average for Batches 1, 2, and 3 in Table 1A, despite the fact that their data is reported in Table 1A (with a one-month average of 22.7 µg/mL). Tr. 774:17-775:8 (Klibanov). It is unclear what information, if any, is intended to be conveyed by the unlabeled line extension.

341. Even if a person reading Figure 3B assumed that the dotted line represented a linear regression extending to the one-month timepoint, he would not assume that it accurately reported the one-month erucic acid results after storage at 25 °C. For instance, plugging one month into the mathematical equation for the 200-

L samples in Figure 3B does not match the true one-month average for the 200-L samples reported in Table 1A. Tr. 428:17-20, 429:8-14 (Schwendeman); Tr. 775:5-25 (Klibanov). A POSA reading Figure 3B would therefore not assume that the 45-L reference samples had a lower erucic acid concentration than the 200-L samples. Tr. 428:21-429:3 (Schwendeman).

342. Pacira's suggested interpretation of Figure 3B is also unsupported by anything in the specification or prosecution history. The description of Figure 3B in the specification of the '495 Patent says nothing about extrapolated values at the one-month timepoint. Tr. 850:10-851:4 (Godici); JTX-4121.11, .20 (4:12-18, 21:34-41). There was no discussion of Figure 3B or how to interpret its extension of the dotted line at any point during prosecution of the '495 Patent. Tr. 653:18-654:4 (Slifer); JTX-4001; JTX-4288.29 (Dai Tr. 255:22-23, 256:04). Indeed, neither the Examiner nor Pacira mentioned Figure 3B at any point during prosecution. Tr. 849:3-6, 850:6-9 (Godici).

343. **Second,** Figure 3B does not comply with the duty to disclose material information to the USPTO from a procedural standpoint, and therefore would not excuse Pacira's concealment of the Los Spreadsheet or Ardekani Data even if it did disclose an extrapolated one-month average for erucic acid. Figure 3B shows (at most) extrapolated averages, without further comment, and would require the Examiner to perform mathematical or graphical analysis that is not described

anywhere in the patent. Tr. 655:5-15 (Slifer). In contrast, the stability data in the Los Spreadsheet and the Ardekani Data clearly and unambiguously indicated that 45-liter batches of EXPAREL® had been measured to have erucic acid concentrations of less than about 23 µg/mL at the one-month timepoint. *Supra* Section III.C.1.a-b. During prosecution of a patent, important material information should be disclosed to the examiner with complete clarity. Tr. 655:16-18 (Slifer). Figure 3B is not an accurate or complete disclosure of the underlying but-for material information, and therefore fails to fulfill the obligation of disclosure under the duty of candor. *Id.*

344. **Third,** any implicit disclosure of one-month averages in Figure 3B (to the extent any such disclosure existed) was concealed by Pacira's affirmative false statements regarding the non-existence of such data and the purportedly "improved stability" of the 200-liter product, as well as Dr. Dai and Ms. Los's explicit arguments that the one-month erucic acid limitation was a purported point of novelty over the prior art. *Supra* Section I.C.2. Examiners are not trained to scrutinize the figures in a patent application for information that contradicts other statements in the specification. Tr. 656:3-7 (Slifer).

345. The fact that Figure 3B failed to disclose the existence of 45-liter batches of EXPAREL® meeting the one-month limitation (or that Pacira's use of "n/a" in Table 1A successfully concealed any such disclosure) was corroborated by

the testimony of Pacira's own inventor. Named inventor Soroush Ardekani agreed that looking at the data on the face of the '495 Patent, no one would know that some of the 45-liter batches had less than 20 µg/mL erucic acid after one month, and was unaware of any disclosure to the USPTO that some of the some of the 45-liter batches had less than 20 µg/mL after one month. JTX-4287.9-10 (Ardekani Tr. 107:9-11, 107:14-15, 107:16-19, 107:22).

346. Pacira's purported reading of Figure 3B also lacks credibility to the extent that it relies on the testimony of Dr. Dai. At deposition, Pacira elicited testimony from Dr. Dai regarding the purported interpretation of Figure 3B—but Dr. Dai did not draft Figure 3B, and there is no evidence that she considered Figure 3B during prosecution (much less interpreted it as Plaintiffs now propose). JTX-4288.4-5, 24-26 (Dai Tr. 61:14-15, 61:22, 63:12-13, 248:13-250:23, 251:5-7, 251:9-13); *infra* ¶ 459. Pacira chose not to elicit any testimony from Ms. Los about the interpretation of Figure 3B, despite the fact that Ms. Los did draft Figure 3B. JTX-4288.4-5 (Dai Tr. 61:14-15, 61:22, 63:12-13); JTX-4289.30 (Los Tr. 144:15-144:24, 145:06-10); JTX-4037.20-21.

347. Ms. Los, who drafted Figure 3B, also provided testimony inconsistent with the idea that Figure 3B was intended to convey an extrapolated one-month average for the 45-liter reference samples. JTX-4289.30 (Los Tr. 144:15-24, 145:6-10, 145:11-25); JTX-4037.20-21. Ms. Los testified that there was "no way" to

"correct mathematically" for the LT 20 values to calculate an average at the one-month timepoint for the 45-liter batches, and that there is "no good way of handling the data when you don't have reportable numbers for some of your data points." JTX-4289.25-26 (Los Tr. 127:18-20, 127:22-24, 128:22-129:7, 129:11-16). Ms. Los did not suggest extrapolation based on a best-fit line as a way to address the "LT 20" values. Ms. Los further testified that the "full data sets" for erucic acid in the patent were only "at 2, 3, and 6 months." JTX-4289.30 (Los Tr. 145:11-25).

348. When shown Pacira's internal data indicating a one-month average lower than 23 µg/mL for 45-liter batches, Ms. Los stated that this data "d[id] seem relevant" to the one-month limitation in the '495 Patent, and that this was the type of information that she would have disclosed to the USPTO if she had considered it. JTX-4289.62 (Los Tr. 268:2-7, 268:11-14, 268:22). This testimony is not consistent with Plaintiffs' litigation theory that Ms. Los believed that Figure 3B showed a one-month average for the reference samples of less than 23 µg/mL, or that this one-month value was irrelevant to novelty.

349. Dr. Dai's contemporaneous prosecution conduct also contradicts Plaintiffs' retroactive interpretation of Figure 3B. On the same day that Dr. Dai filed the application for the '495 Patent, she filed the application for the '494 Patent, directed to a "composition claim, containing the erucic acid concentration [of] about 23-microgram per milliliter after the composition is stored at the 25 degrees C for

one month," the same erucic acid concentration limitation as claim 1 of the '495 Patent. JTX-4288.22-23 (Dai Tr. 228:25-229:2, 229:6-15, 231:6-9, 231:12-20); JTX-4130.1, .22. Claim 1 of the '494 Patent had no other purportedly novel physical properties—much like the '495 Patent, it is directed to a "composition of bupivacaine encapsulated multivesicular liposomes (MVLs)" with "bupivacaine residing inside a plurality of internal aqueous chambers . . . separated by lipid membranes," where those membranes comprise DEPC and DPPG "and at least one neutral lipid," and "an aqueous medium in which the bupivacaine encapsulated MVLs are suspended," none of which was novel over prior art EXPAREL®. JTX-4130.22 ('494 patent claim 1); *supra* Section II.A. This conduct is inconsistent with any argument that Pacira's decisions during prosecution of the '495 Patent were driven by a belief (1) that the novelty of the claimed composition lay anywhere other than the one-month erucic acid limitation, or (2) that the USPTO was aware based on Figure 3B that the one-month erucic acid concentration was not novel.

350. **Fourth**, any argument regarding purported "cumulativeness" of the withheld one-month data ignores the fact that Pacira also withheld data that showed anticipation of claims 3, 5, and 7, with limitations to erucic acid concentration at the two-, three-, and six-month timepoints as well as the one-month timepoint. *Supra* Section III.C.1.

351. Because Figure 3B reports only 2, 3, and 6-month averages, a POSA could not figure out the 1, 2, 3, and 6-month results for any individual batch from Figure 3B. Tr. 429:4-14 (Schwendeman); Tr. 777:1-778:14 (Klibanov). Even if Figure 3B did disclose an extrapolated one-month average for erucic acid, it would not obviate the need to disclose individual 45-liter batch data. Tr. 654:19-655:2 (Slifer). The dependent claims require specified erucic concentrations at one month ***and*** two, three, or six months. JTX-4121.21 ('495 Patent claims 3, 5, and 7). From the averages in Figure 3B, the Examiner could not determine whether any individual batches of 45-liter EXPAREL met these limitations at multiple timepoints. Tr. 655:19-656:2 (Slifer); Tr. 777:1-778:14 (Klibanov).

352. The MPEP instructs examiners and applicants that "references may be highly material when they disclose a more complete combination of relevant features, even if the individual features have already been disclosed." Tr. 857:8-24 (Godici); DTX-2200.11 (MPEP Chapter 2200). While the tables in the '495 Patent present only average values for erucic acid and external pH over time for the 45-liter batches (JTX-4121.19-20 (Tables 1A, 1B, 2A, and 2B)), the Los Spreadsheet and the Ardekani Data disclose individual batch data. JTX-4037.18-19; Tr. 857:25-858:15, 860:2-25 (Godici); DTX-2465.4-19, .42, .44, .45, .47, .50, .52, .57, .59, .65, .67. This information is relevant to dependent claims 2-8 of the '495 Patent, which contain limitations to specific erucic acid levels and/or external pH over time for

individual compositions. Tr. 858:24-859:16 (Godici); JTX-4121.20-21. As such, the data withheld by the applicants disclosed a "more complete combination of features" for the 45-liter reference batches than any disclosures in the specification. Tr. 861:1-6 (Godici).

353. Because the Los Spreadsheet and the Ardekani Data contain individual batch data that shows the existence of individual 45-liter batches of EXPAREL® with erucic acid concentrations within the claimed ranges at the one-, two-, three-, and six-month timepoints, they would be non-cumulative and but-for material to at least claims 3, 5, and 7 even if Figure 3B disclosed the existence of batches meeting the one-month limitation.

2. Pacira's False and Misleading Statements During Prosecution Were But-For Material

a. Pacira's False and Misleading Statements Concealing the Existence of One-Month Erucic Acid Data Were But-For Material

(1) Pacira Made False, Misleading, and But-For Material Statements Concealing the Existence of Anticipatory One-Month Erucic Acid Data

354. As discussed above, during prosecution, Dr. Dai and Ms. Los were in possession of data indicating that multiple batches of 45-liter EXPAREL® had a concentration of less than about 23 µg/mL after storage for one month at 25 °C, and never provided this data to the USPTO during prosecution. *Supra* Section III.C.1; *infra* Section III.D.2. Instead, Dr. Dai and Ms. Los affirmatively concealed the

existence of this data by falsely representing to the USPTO that no one-month data existed for the 45-liter "reference samples" in the '495 Patent.

355. The supposedly "improved stability" of the compositions claimed in the '495 Patent is purportedly illustrated by Example 1A of the patent, with data on erucic acid over time set forth in Table 1A for Batches 1, 2, and 3 (i.e., the 200-liter batches) and ten "reference samples" (i.e., the 45-liter batches). *Supra* Section I.C.1.

356. Table 1A of the '495 Patent contains data on erucic acid levels in batches of EXPAREL® after 1, 2, 3, and 6 months of storage at 25 °C. Specifically, Example 1 states that Table 1A contains individual batch values for three batches of EXPAREL® "prepared by the new process described herein" at each of these time points, and that it purportedly contains average values for "ten reference samples . . . prepared by the current commercial process" at the 2, 3, and 6-month timepoints. JTX-4121.19 (20:28-67).

357. In reality, Table 1A reflects erucic acid measurements for three batches of EXPAREL® produced using a 200-liter manufacturing process at each timepoint, and average values for only seven 45-liter batches of EXPAREL® at the two-, three-, and six-month timepoints. JTX-4121.19 (20:49-67); *supra* ¶ 22. For the one-month time point in Table 1A, the table lists only "n/a" for the 45-liter batches rather than any numerical value. JTX-4121.19 (20-49-67).

358. A POSA would have understood the "n/a" in Table 1A to mean that data did not exist at the one-month timepoint for the 45-liter reference batches. For instance, named inventor Dr. Ardekani testified that as a scientist, he would never use "n/a" in a data table if data was in fact available, and would interpret "n/a" to mean that the data did not exist. JTX-4287.11 (Ardekani Tr. 116:22-23, 116:25, 117:15-19, 117:22-118:1, 118:3-5). Ms. Los, another named inventor, used "NA" in the Los Spreadsheet to mean that data did not exist for some batches at the six-month timepoint, and agreed that the "n/a" in Table 1A could be read as indicating that data was unavailable for the 45-liter reference samples at the one-month timepoint. JTX-4289.23, 39-40 (Los Tr. 124:11-22, 124:24, 171:3-4, 171:7-10, 172:11-14, 172:16-18, 172:19-25, 173:02); JTX-4037.18. Dr. Schwendeman, as a scientific expert, also understood "n/a" in Table 1A as indicating that data was not available at that timepoint. Tr. 426:18-23 (Schwendeman).

359. Because Pacira was in possession of data at the one-month timepoint, this use of "n/a" in Table 1A was therefore false and misleading. The false and misleading use of "n/a" was particularly egregious because Pacira's data at the one-month timepoint, which Pacira told the USPTO did not exist, actually showed that multiple prior art batches of 45-liter EXPAREL® met the purportedly novel one-month erucic acid limitation. *Supra* Section III.B.

(2) Pacira's Excuses for Its False and Misleading Statements Concealing Anticipatory One-Month Data Are Implausible and Insufficient

360. At trial, Pacira offered the excuse that the "n/a" in Table 1A was not misleading, because it was impossible to calculate a precise numerical average for the 45-liter reference samples due to the "LT 20" values for some of the batches. Tr. 754:23-755:13 (Klibanov); JTX-4289.24-25 (Los Tr. 127:6-10, 127:12-20, 127:22-128:2, 128:5-8); DTX-2176.30 ("Because at the 1-month time point, 3 of the lots had concentrations of erucic acid that were below the limit of detection (LT 20), 'n/a' was listed in Example 1A at that time point."). This purported explanation does not save the "n/a" in Table 1A from being false and misleading.

361. **First**, Pacira's witnesses and its Interrogatory response admit that the use of "n/a" in Table 1A was an intentional decision based on the fact that three of the 45-liter reference samples had less than 20 µg/mL at the one-month timepoint—i.e., the fact that three of the 45-liter reference samples anticipated Claim 1. Tr. 754:23-755:13 (Klibanov); JTX-4289.24-25 (Los Tr. 127:6-10, 127:12-20, 127:22-128:2, 128:5-8); DTX-2176.30 ("Because at the 1-month time point, 3 of the lots had concentrations of erucic acid that were below the limit of detection (LT 20), 'n/a' was listed in Example 1A at that time point."). Pacira's purported "explanation" only underscores the fact that the use of "n/a" in Table 1A was an intentional decision based on the existence of undisclosed anticipatory data.

362. **Second**, Pacira's purported explanation for the "n/a" in Table 1A was not available to the Examiner during prosecution—it is based entirely on Ms. Los's after-the-fact litigation testimony, and unsupported by (and indeed, inconsistent with) contemporaneous evidence.

363. As the inventors admitted, the "n/a" in Table 1A would typically be read as an indication that no data existed at that timepoint, and no further explanation was provided in the '495 Patent itself. JTX-4287.11 (Ardekani Tr. 116:22-23, 116:25, 117:15-19, 117:22-118:1, 118:3-5); JTX-4289.17, 23, 39-40 (Los Tr. 85:14-16, 85:18, 124:11-22, 124:24, 171:3-4, 171:7-10, 172:11-14, 172:16-18, 172:19-25, 173:02). Indeed, Pacira later decided to add a footnote to Table 1A in some of its related patents explaining its unconventional use of "n/a"—though only in patents with no claims involving the one-month concentration of erucic acid. *Infra* Section III.D.3.a. As such, Pacira's "explanation" is irrelevant to whether the use of "n/a" in Table 1A was objectively false and misleading, as this "explanation" was not available to the USPTO during prosecution.

364. Pacira's purported "explanation" of the drafting decisions for Table 1A also lacks credibility because it was offered exclusively through Ms. Los—who did not draft Table 1A. At deposition, Pacira allowed Ms. Los to offer a purported explanation of the decision to include "n/a" in Table 1A rather than a one-month value, despite the fact that Ms. Los did not draft Table 1A. JTX-4289.38-39 (Los

Tr. 168:19-169:19); DTX-2176.30. Pacira did not offer any testimony in support of this excuse from Dr. Dai, the person who actually drafted Table 1A and who made the final determination as to which information should be included. Tr. 343:5-15 (Molloy); *infra* Section III.D.2.

365. **Third**, even if Pacira's explanation for why it used "n/a" was accurate, the use of "n/a" in Table 1A would still be objectively false and misleading. "N/a" may can be used in data tables to indicate that data is not applicable or not available, but it is not the appropriate format to indicate that some of the 45-liter batches had values of "LT 20." Tr. 426:24-427:10 (Schwendeman). Appropriate alternatives would include putting estimates or a description of the meaning of "n/a" (like the description Pacira belatedly added in some of its subsequent applications), or reporting all individual data points. *Id.* Named inventor Ms. Los agreed that it would have been possible to report individual batch values for the 45-liter reference samples in the '495 Patent, rather than merely averages. JTX-4289.26 (Los Tr. 129:17-19, 129:23).

366. As discussed above, the one-month data in Pacira's possession indicated that independent claim 1 was anticipated by prior art batches of EXPAREL®, as well as contributed to a showing of anticipation for dependent claims 3, 5, and 7 based on Pacira's additional undisclosed data. *Supra* Section III.C.1. Pacira's use of "n/a" in Table 1A falsely stated that one-month data for 45-

liter batches of EXPAREL® did not exist, affirmatively concealing the existence of anticipatory prior art in its possession. As such, the false and misleading use of "n/a" in Table 1A was but-for material to the issuance of at least claims 1, 3, 5, and 7 of the '495 Patent.

b. Pacira's False and Misleading Representations of "Improved Stability" Were But-For Material

367. In the specification of the '495 Patent and during prosecution, Pacira repeatedly represented to the USPTO that the claimed composition had "improved stability" compared to prior art 45-liter EXPAREL®. *Supra* ¶ 33. As explained below, Pacira's representations of "improved stability" to the USPTO were false and misleading, and were but-for material to the issuance of the '495 Patent.

368. The specification of the '495 Patent states that the purportedly "new and improved" process "yields a more stabilized form of bupivacaine encapsulated MVLs, having less lipid degradation byproducts [i.e., erucic acid]"; that the new product had "improved stability over the commercial Exparel® product"; and that the new product had "lower lipid hydrolysis byproducts [i.e., erucic acid] compared to the commercial Exparel® product under the same incubation condition." JTX-4121.11, .13 (4:28-40, 13:49-55). The specification further states that "[t]he improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected." *Id.* at JTX-4121.20 (21:52-55).

369. During prosecution, the Examiner initially rejected all claims as obvious under 35 U.S.C. § 103 based on two publicly available references, Camu and Li. Tr. 637:22-639:19 (Slifer); Tr. 842:21-843:9 (Godici); JTX-4001.2146-2151. On April 16, 2021, Dr. Dai participated in a telephone interview with the Examiner discussing his rejection of independent Claim 1, which had the one-month erucic acid limitation. JTX-4001.2167. In this interview, Dr. Dai argued that Claim 1 was patentable because the prior art did not "teach the amount of erucic acid concentration ***after one month*** as the product by process is ***more stable*** than the cited art combination." *Id.* (emphasis added). Based on Dr. Dai's argument that the claimed process resulted in a "more stable" product at the one-month timepoint, the Examiner requested "a declaration of why one skilled in the art would not expect the prior art to have ***the same claimed acid concentration***"—i.e., an erucic acid concentration of "about 23 μg/mL or less" after one month of storage at 25 °C. *Id.* (emphasis added).

370. On April 22, 2021, Dr. Dai filed an applicant response, attaching a declaration from named inventor Ms. Los (the Los Declaration). Tr. 643:4-12 (Slifer); JTX-4001.2175-80. In that applicant response, Dr. Dai argued to the Examiner that Pacira's "new commercial process yields a bupivacaine MVL product with ***superior stability*** as compared to the product made by the prior process," and that the "new" composition had "demonstrated less lipid membrane degradation, as

measured by . . . erucic acid . . . over a period of 6 months at 25 °C." JTX-4001.2176 (emphasis added). Dr. Dai relied on the Los Declaration to support these factual claims. *Id.* In view of this purportedly "improved stability," Dr. Dai argued that neither Camu nor Li disclosed a composition with an erucic acid concentration of "about 23 μg/mL or less" after storage at 25 °C for one month. *Id.*

371. In support of Dr. Dai's applicant response, Pacira submitted the Los Declaration on the same day. In her Declaration, Ms. Los also stated that "new commercial process yields a bupivacaine MVL product with ***superior stability*** as compared to the product made by the prior process," and that the "new" composition had "demonstrated less lipid membrane degradation, by measuring . . . erucic acid . . . over a period of 6 months at 25 °C." *Id.* at 2179. Ms. Los further stated that the "new" product was "expected to have a shelf life of up to 2 years . . . at 5°C," but did not mention that this was the same shelf life as prior art EXPAREL®. *Id.*; Tr. 648:8-21 (Slifer); *see also* Tr. 453:7-15 (Schwendeman); Tr. 766:9-14 (Klibanov); JTX-4205; DTX-3115. In the same Declaration, Ms. Los argued that the prior art did not teach "the erucic acid level recited in instant claims"—i.e., the one-month erucic acid limitation for all claims, and the two-, three-, and six-month erucic acid limitation for certain dependent claims. JTX-4001.2180.

(1) Pacira's Statements Regarding "Improved Stability" Were False, Misleading, and But-For Material

372. The statements in the patent specification, Dr. Dai's applicant response, and the Los Declaration that the 200-liter process results in a product with "improved stability" were false and misleading for several reasons. Tr. 435:9-436:24 (Schwendeman).

373. **First**, Dr. Dai and Ms. Los's statements regarding "improved stability" were false and misleading because the claimed erucic acid concentrations were not novel; rather, they were anticipated by the Prior Art EXPAREL® Product, as shown by the data in the Los Spreadsheet and the Ardekani Data (as well as other data at Pacira).

374. During prosecution, all communications between the Examiner and Pacira were focused on the one-month erucic acid limitation in independent claim 1 of "about 23 μg/mL or less." *Supra* Section I.C.2. The focus on claim 1 was consistent with standard USPTO policy and procedure, as claim 1 was (and as issued is) the only independent claim the '495 Patent. Tr. 640:18-24 (Slifer). In context, the statements by Dr. Dai and Ms. Los regarding "improved stability" would have therefore been understood to imply that the "new" product had lower concentrations of erucic acid at the one-month timepoint than prior art EXPAREL®, and that the

claimed one-month concentration of "about 23 µg/mL or less" of erucic acid represented an improvement in stability over the prior art.

375. Dr. Dai's and Ms. Los's representations of "improved stability" were therefore false and misleading, because Pacira's 200-liter batches did not have lower erucic acid concentrations at the one-month timepoint than its 45-liter batches, and the claimed one-month concentration of "about 23 µg/mL or less" of erucic acid was not novel. At the one-month timepoint, multiple batches of prior art EXPAREL® had an erucic acid concentration of "about 23 µg/mL or less," as indicated by the undisclosed data in the Los Spreadsheet. *Supra* Section III.C.1.a.

376. Although the focus during prosecution was on the one-month limitation, Dr. Dai and Ms. Los's representations of "improved stability" were also false and misleading with respect to the two-, three-, and six-month timepoints in certain dependent claims, for the same reason. Multiple batches of prior art EXPAREL® had the claimed concentration of erucic acid at the two-month timepoint (claim 3) and the three-month timepoint (claim 5) as well as the one-month timepoint (claim 1), as reflected in the Los Spreadsheet. *Supra* Section III.C.1.a . Approximately one third of prior art EXPAREL® batches also had the claimed concentration of erucic acid at the six-month timepoint based on Pacira's historical data, consistent with the undisclosed 45-liter Swindon batches in the Ardekani Data. Tr. 435:9-436:24 (Schwendeman); *supra* Section II.A.4. The erucic acid levels of

the 200-liter product reported in the '495 Patent were therefore not novel at any timepoint compared to the Prior Art EXPAREL® Product (made by the 45-liter process), and Dr. Dai and Ms. Los's representations of "improved stability" were objectively false and misleading.

377. Pacira's regulatory submissions confirm that the representations of "improved stability" during prosecution were false. Pacira told the FDA that the increases in erucic acid levels for its 200-liter batches were "consistent with EXPAREL lots on stability manufactured at 45-liter scale over 6 months," and that "[t]he stability data collected over nine months from EXPAREL registration lots manufactured with the 200-liter bulk manufacturing process at Swindon confirm the material is equivalent to the drug product manufactured by the approved 45-liter process." Tr. 441:21-443:7 (Schwendeman); JTX-4187.4. These statements were true, but contradictory to what Pacira told the USPTO. Tr. 441:21-443:7 (Schwendeman); JTX-4187.4.

378. **Second**, Pacira's statements regarding "improved stability" were additionally false and misleading because two of the three 200-liter batches reported in the '495 Patent actually *failed* to meet Pacira's required shelf-life specifications—specifically, the d_{90} particle size specification. Tr. 437:20-439:2 (Schwendeman); JTX-4188.11.

379. **Third**, the Los Declaration stated in its paragraph discussing purportedly "superior stability" that the 200-liter product was "expected to have a shelf life of up to 2 years when properly handled and stored at 5°C." JTX-4001.2179; *see also* JTX-4121.11 (4:62-65) (identifying the "shelf life of the product" as "up to 2 years when stored at 2-8°C"). While this statement was factually true in isolation, it was incomplete and misleading in the context of Ms. Los's discussion of purportedly "superior stability." Far from indicating "superior stability," the two-year refrigerated shelf life of 200-liter batches of EXPAREL® meant that those batches were expected to have the ***same*** shelf life as prior art 45-liter EXPAREL®, suggesting that there was in fact no meaningful difference in stability. Tr. 454:6-14 (Schwendeman); Tr. 767:9-14 (Klibanov); JTX-4205.27; DTX-3115.37; *supra* Section II.B.2, Section II.C.2. In her Declaration, Ms. Los omitted the fact that this two-year shelf life was identical to the shelf life of prior art EXPAREL®. Tr. 648:8-21 (Slifer); JTX-4001.2178-80.

380. Pacira's false and misleading statements regarding "improved stability" were but-for material to the issuance of the '495 Patent. In particular, Dr. Dai's and Ms. Los's statements regarding "improved stability" in the April 22, 2021 Applicant Remarks and Los Declaration were made in direct response to the Examiner's rejection of the claims, and Pacira relied on those representations to argue for the novelty of the claims based on the one-month erucic acid limitation. *Supra* Section

I.C.2. The Examiner explicitly relied on this argument and the Los Declaration for issuance of the '495 Patent, stating that he "f[ound] the [Los] [D]eclaration persuasive" to support that the prior art did not teach compositions "having the claimed storage stability." JTX-4001.2311; *supra* ¶ 39.

(2) Pacira's Excuses for Its False and Misleading Statements Regarding "Improved Stability" Are Implausible and Insufficient

381. Pacira has implied that its statements to the USPTO touting the "improved stability" of the 200-liter product were limited to the six-month timepoint, and were therefore accurate. Tr. 842:14-20 (Godici); JTX-4288.6-7 (Dai Tr. 88:09-10, 88:11-12, 88:16, 88:23-89:12, 89:15-16, 89:17-19, 89:22-23); D.I. 298 Tab 9 (Plaintiffs' Contested Facts) at 57. Pacira bases this argument on the fact that Dr. Dai and Ms. Los referred to lower erucic acid concentrations "over a period of six months," and the Examiner's statement in his Reasons for Allowance that the prior art did not teach "the claimed degradation product of erucic acid after 6 months storage at 25C." JTX-4001.2176, .2179, .2311; Tr. 842:14-20 (Godici); D.I. 298 Tab 9 (Plaintiffs' Contested Facts) at 57. As discussed below, this retroactive interpretation of Pacira's statements does not make sense. Further, even if this interpretation were adopted, it would not save Pacira's statements from being false and misleading.

382. **First**, interpreting Pacira's statements regarding "improved stability" to be limited to the six-month timepoint makes no sense in context. Neither the statements in the specification nor the statements during prosecution were limited as to timepoint; to the extent that the specification or Examiner focused on any particular timepoint, it was the one-month timepoint, not the six-month timepoint. *Supra*, Section I.C.2.

383. The patent specification focuses primarily on embodiments of the claimed invention "wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25°C for one month." JTX-4121.10 (2:19-67). The only independent claim, claim 1, has the one-month erucic acid limitation; only two of the patent's 22 claims recite the six-month erucic acid limitation. JTX-4121.20-21; Tr. 634:16-636:18 (Slifer); JTX-4001.17-19. None of the statements in the specification regarding "improved stability" state or imply that the "improved stability" can only be found at the six-month timepoint. JTX-4121.4 (4:26-40) ("[T]he improved and scaled up process also yields a more stabilized form of bupivacaine encapsulated MVLs, having less lipid degradation byproducts . . . ."), .16 (13:49-51) ("The bupivacaine MVLs produced by the process described herein have improved stability over the commercial Exparel® product."), .20 (21:51-55) ("The improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently

described process was surprisingly unexpected."); JTX-4288.6-7 (Dai Tr. 88:09-10, 88:11-12, 88:16, 88:23-89:12, 89:15-16, 89:17-19, 89:22-23).

384. During prosecution, all discussion and correspondence between the Examiner and Pacira was primarily focused on the novelty of claim 1 and its one-month erucic acid limitation, not the six-month erucic acid limitation; and for good reason—claim 1 was the only independent claim, and most of the pending claims did not require the six-month erucic acid limitation. *Supra* Section I.C.2.

385. In this context, Dr. Dai and Ms. Los told the Examiner that Pacira's "new" 200-liter process "yields a bupivacaine MVL product with superior stability as compared to the product made by the prior process," and that the new composition "demonstrated less lipid membrane degradation, as measured by . . . erucic acid . . . over a period of 6 months at 25 °C." JTX-4001.2176, 2179. In the same submissions, Dr. Dai and Ms. Los argued that the one-month erucic acid limitation distinguished the claimed composition from the prior art. *Supra* Section I.C.2. In context, the natural interpretation of Dr. Dai's and Ms. Los's statements was that erucic acid had been measured "over a period of 6 months at 25 °C"—i.e., that erucic acid had been measured at one, two, three, and six months, as reflected in Example 1 of the specification (JTX-4121.19 (20:38-45))—and that the 200-liter batches had shown "superior stability" at all timepoints in the form of lower concentrations of erucic acid.

386. Nor does the Examiner's statement of Reasons for Allowance indicate that he relied only on the six-month timepoint, as Pacira now argues. JTX-4001.2311; Tr. 842:14-20 (Godici). Such an interpretation of the Reasons for Allowance would make no sense: all of 22 of the claims of the '495 Patent incorporate the one-month limitation (including Claim 1, the only independent claim), and only two of the claims incorporate the six-month limitation (claims 7 and 8). Tr. 652:15-653:2 (Slifer); JTX-4001.2311. For its creative interpretation of the prosecution statements, Pacira relies on the Examiner's brief summary of the Los Declaration as attesting that the prior art "fails to teach the claimed degradation product of erucic acid after 6 months storage at 25 °C." JTX-4001.2311; Tr. 842:14-20 (Godici). However, Pacira ignores the Examiner's ultimate finding that, based on the Los Declaration, his understanding was that the prior art did not teach MVLs "having the ***claimed storage stability***"—i.e., the one-month limitation for Claim 1 and all dependent claims, as well additional timepoints for a few dependent claims. JTX-4001.2311 (emphasis added); JTX-4121.20-21. Read as a whole, the Examiner's Reasons for Allowance make it clear that the Examiner understood Pacira's statements regarding "superior stability" according to their most natural interpretation: that the 200-liter product had lower erucic acid concentrations at the one-month, two-month, three-month, ***and*** six-month timepoints.

387. Mr. Godici agreed that sometimes the USPTO issues a patent that should not have been issued, and that this may happen where there was additional information available that the examiner was not aware of. Tr. 864:13-21 (Godici). Any interpretation of the Reasons for Allowance that ignores the fact that the Examiner was presented with incomplete data and misleading statements is unpersuasive.

388. **Second**, even if Dr. Dai and Ms. Los had intended their statements to refer only to the six-month timepoint (and there is no evidence that they did), submitting these statements to the Examiner would still have been misleading and a violation of the duty of candor. In the context of previous prosecution events, it would have made no procedural sense to submit an inventor declaration that was limited to discussion of only the six-month timepoint. Tr. 647:13-648:7 (Slifer); JTX-4001.2179. The Examiner was primarily focused on the patentability of claim 1, with its one-month erucic acid limitation, as were Dr. Dai's and Ms. Los's submissions. *Supra* Section I.C.2. At best, according to Pacira's own interpretation of events, Dr. Dai and Ms. Los submitted USPTO filings referring generally to "improved stability" to overcome the Examiner's claim 1 rejections and used those filings to argue for the novelty of the one-month erucic acid limitation, with the private belief that "improved stability" had only been observed at the six-month timepoint (and not any earlier timepoints). Such conduct would not comply with the

duty of candor, whether or not Dr. Dai and Ms. Los crafted their statements such that portions could be read to apply only to the six-month timepoint.

389. **Third**, Dr. Dai and Ms. Los's statements would have been factually false and misleading even if limited to the six-month timepoint. As discussed below, the '495 Patent's reported difference at the six-month timepoint would have lacked any practical significance, even if such a difference truly existed between 200-liter EXPAREL® and prior art 45-liter EXPAREL® (which it did not; *see supra* Section II.B.2; Section II.C.2).

390. Pacira's representations in the specification regarding "improved stability" were presented in the context of arguing to the USPTO that 200-liter EXPAREL® had unexpectedly superior stability as compared to prior art 45-liter EXPAREL®. *See* JTX-4121.20 (21:52-55) ("The improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected.").

391. The same is true of Pacira's statements regarding "improved stability" during prosecution. These statements were introduced in Ms. Los's Declaration under 37 C.F.R. § 1.132 in response to the Examiner's *prima facie* obviousness rejection and Dr. Dai's applicant response (which relied on the statements in the Los Declaration). JTX-4001.2176, .2178-79; *supra* Section I.C.2.

392. Pursuant to USPTO policy, applicants may overcome an Examiner's *prima facie* case of obviousness through such a declaration by presenting evidence that the claimed invention is superior in a property that is shared with the prior art—here, Pacira's representations of purportedly "improved stability" as measured by erucic acid, compared to prior art EXPAREL®. JTX-4001.2176, 2178-79; Tr. 863:5-864:12 (Godici); DTX-3099.247-48 (MPEP Ch. 700). However, in order to overcome a rejection on this basis, the applicant must present differences and results that are "in fact unexpected and unobvious ***and of both statistical and practical significance***." DTX-3099.247-48 (MPEP Ch. 700); Tr. 863:5-864:12 (Godici).

393. In context, Pacira's statements regarding "improved stability" implied that the reported differences in erucic acid concentration had "both statistical and practical significance," as required by the MPEP for a showing of unexpected superiority to overcome obviousness. DTX-3099.247-48 (MPEP Ch. 700); Tr. 863:5-864:12 (Godici).

394. As Ms. Los testified, her team performed no analysis as to whether the reported differences were even statistically significant, let alone practically significant. JTX-4289.32 (Los Tr. 155:3-6, 155:8-9, 155:15-16).

395. In fact, as discussed below, there was no practical significance to the differences in erucic acid concentration reported in the '495 Patent, including the differences reported at the six-month timepoint. The differences in six-month erucic

acid concentrations reported in the '495 Patent and the Los Spreadsheet are too small to have any practical impact on the properties of the drug product. Moreover, the six-month timepoint at 25 °C is irrelevant to stability for EXPAREL® over its two-year refrigerated shelf life.

396. In this context, Pacira's statements regarding "improved stability" were therefore false and misleading even if limited to the six-month timepoint, and even if limited to the data in the '495 Patent and Los Spreadsheet (rather than considering, e.g., the Ardekani Data).

397. The difference in six-month erucic acid values reported in the '495 Patent specification and the Los Spreadsheet is 99 µg/mL for the 200-liter batches, compared to 110-115 µg/mL for most of the 45-liter batches. JTX-4037.18; JTX-4121.19 (Table 1A). A POSA would have expected that batches with 99 µg/mL after six months of storage at 25 °C would have the same or similar properties as batches with 110 to 115 µg/mL. Tr. 426:24-454:4 (Schwendeman). 99 µg/mL is not an important threshold for stability, as evidenced by Pacira's erucic acid shelf life specification of no more than 310 µg/mL. Tr. 457:1-20 (Schwendeman); JTX-4057.29.

398. As Pacira told the FDA, and as Ms. Los was aware, erucic acid levels of up to 310 µg/mL (approximately 10% degradation of DEPC) do not impact the pharmacokinetic profile of EXPAREL, and would not have been expected to impact

product performance. Tr. 457:21-459:10 (Schwendeman); JTX-4264.5; JTX-4289.64-66 (Los Tr. 284:15-23, 285:1-14, 285:18-23, 285:25-286:3, 288:13-289:1, 289:4-289:11, 289:15-289:20, 289:24-25); DTX-2438.1, DTX-2437.1. The difference between 99 µg/mL and 110-115 µg/mL would therefore not be expected to have any impact on the properties of EXPAREL. Tr. 457:12-16 (Schwendeman); JTX-4289.64-66 (Los Tr. 284:15-23, 285:1-14, 285:18-23, 285:25-286:3, 288:13-289:1, 289:4-289:11, 289:15-289:20, 289:24-25); DTX-2438.1; DTX-2437.1.

399. Additionally, any "improved stability" limited to the six-month timepoint would have had no practical relevance regardless of its magnitude, because the erucic acid concentration in EXPAREL® after six months of storage at 25 °C is not predictive of its erucic acid concentration at any point during its two-year refrigerated shelf life. Tr. 768:1-769:4 (Klibanov); *see also* JTX-4004; JTX-4007; JTX-4057; JTX-4264.

400. EXPAREL® is intended for storage under refrigerated conditions. Tr. 81:22-82:2 (Hall); Tr. 154:19-24 (Grigsby). Under its intended refrigerated storage conditions, EXPAREL® has a two-year shelf life, which is the same regardless of whether it is manufactured using Pacira's 45-liter manufacturing process or its 200-liter manufacturing process. Tr. 86:15-23 (Hall); Tr. 454:5-8 (Schwendeman). EXPAREL®'s approved label as of November 2023 (i.e., after the introduction of Pacira's 200-liter process) has only one set of storage instructions for all batches,

instructing that vials must be stored "refrigerated between 2°C to 8°C" and that EXPAREL® "may be held at a controlled room temperature of 20°C to 25°C . . . for up to 30 days in sealed, intact (unopened) vials." DTX-3115.1, 37; *see also* Tr. 83:6-84:7 (Hall); Tr. 154:19-24 (Grigsby).

401. As the '495 Patent indicates, the claimed composition has a shelf life of "up to two years" when stored under refrigerated conditions—the same as prior art EXPAREL®. JTX-4121.11 (4:62-65); *supra* ¶ 179. For EXPAREL®, six-month data from accelerated stability testing at 25 °C is not predictive of EXPAREL®'s erucic acid levels by the end of its shelf life under normal storage conditions (i.e., two years of storage at 2-8 °C). Tr. at 193:14-22 (Grigsby). In fact, six-month erucic acid levels after storage at 25 °C are much higher than the levels observed after two years of refrigerated storage. Tr. at 193:14-22 (Grigsby).

402. Shelf-life values of erucic acid can be predicted by two-month or three-month values at 25 °C—but not by six-month values. As Pacira told the FDA, three-month erucic acid values at 25 °C are predictive of erucic acid values for over two years under refrigerated conditions. Six-month erucic acid levels at 25 °C are much higher, and do not correlate with erucic acid concentration during the product's shelf life. Tr. 454:15-455:25 (Schwendeman); Tr. 769:1-770:2 (Klibanov); JTX-4004.1; *see also* Tr. 456:2-21 (Schwendeman); JTX-4007.1 ("[H]istorically 6 month 25C hasn't been shown to correlate to any real time shelf life or stability and is an

unnecessary time point."). Based on Pacira's data, the Arrhenius correlation predicts that two- or three-month data at 25 °C would correlate with 24 months at 5 °C for EXPAREL—not six-month data at 25 °C. Tr. 769:1-770:2 (Klibanov); JTX-4004.1.

403. The fact that six-month erucic acid data at 25 °C does not correlate to 24-month erucic acid data at 5 °C is also evident from the Ardekani Data, as is the fact that 45-liter prior art EXPAREL® remained far below Pacira's 310 µg/mL specification for erucic acid throughout refrigerated storage for 24 months. *See, e.g.*, DTX-3110; DTX-2465.

404. For instance, for Lot 16-3090, the Ardekani Data included both the 5 °C and the 25 °C erucic acid stability data. Tr. 767:4-768:1 (Klibanov); DTX-2465.51-52. After 24 months at 5 °C, Lot 16-3090 had only 34 µg/mL erucic acid, corresponding roughly to the 2-month result at 25 °C (36 µg/mL). Tr. 767:4-768:1 (Klibanov); DTX-2465.51-52. The erucic acid at the end of shelf life under refrigerated conditions was therefore much lower than the 6-month result at 25 °C of 114 µg/mL. Tr. 767:4-768:1 (Klibanov); DTX-2465.51-52. For Lot 16-3089, the Ardekani Data also included both the 5 °C and the 25 °C erucic acid stability data. Tr. 768:2-18 (Klibanov); DTX-2465.49-50 (Ardekani Data). After 24 months of refrigerated storage, the erucic acid was only 35 µg/mL, corresponding roughly to two months at 25 °C (34 µg/mL).

405. For at least the reasons above, Pacira's statements to the USPTO regarding "improved stability" were false and misleading even if they applied only to the six-month timepoint (which they did not). These statements would also have been but-for material even if limited to the six-month timepoint—for all claims, because in context the Examiner would have interpreted them as covering all timepoints. At a minimum, the statements would have been but-for material to the issuance of claims 7 and 8 even if the Examiner understood them to be limited to the six-month timepoint, because (1) there was no true difference between 200-liter and 45-liter EXPAREL® at the six-month timepoint, as shown by Pacira's undisclosed data (such as the Ardekani Data) (*supra* Section II.B.2, Section II.C.2, Section III.B.2), and (2) to the extent there was any such difference, it was not a difference of "statistical and practical significance" sufficient to overcome the Examiner's *prima facie* showing of obviousness. *Supra* Section III.A.3.

c. Pacira's False and Misleading Statements Regarding Bupivacaine Concentration Were But-For Material

406. During prosecution of the '495 Patent, Dr. Dai additionally argued against the Examiner's rejection of claim 1 of the '495 Patent on the grounds that the claimed process purportedly "allow[ed] higher concentrations of bupivacaine"—i.e., a "target concentration from about 12.6 mg/mL to about 17.0 mg/mL." JTX-4001.2167, 2179; Tr. 640:25-641:24 (Slifer). In response to this argument, the

Examiner requested that claim 1 be amended to include this purportedly higher concentration of bupivacaine. JTX-4001.2167; Tr. 640:25-641:24 (Slifer).

407. In Pacira's responsive submission on April 22, 2021, Dr. Dai amended claim 1 of the application to add a limitation requiring a "target concentration" of bupivacaine "from about 12.6 mg/mL to about 17.0 mg/mL." consistent with her telephone interview with the Examiner. *Id.* at 2171; Tr. 641:25-643:3 (Slifer). In the Applicant Remarks and the Los Declaration submitted on the same day, Dr. Dai and Ms. Los both stated that "[t]he bupivacaine MVLs manufactured by the claimed process ha[ve] a target concentration of bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL," and argued that this limitation was not taught by the Examiner's prior art references. JTX-4001.2176, 2179-80; Tr. 648:22-649:23 (Slifer).

408. In reality, the concentration of bupivacaine in Pacira's 200-liter product is not "higher" than the prior art—it is the same, 13.3 mg/mL. *Supra* ¶¶ 64. In their statements highlighting the concentration of bupivacaine in Pacira's 200-liter process, Dr. Dai and Ms. Los omitted that this concentration of bupivacaine was the same as prior art 45-liter EXPAREL®. Tr. 643:13-644:2, 648:8-21 (Slifer); JTX-4001.2167, 2176, 2179-80. Dr. Dai's statement to the Examiner that the claimed process "allow[ed] higher concentrations of bupivacaine" than the prior art was therefore false, or at a minimum, incomplete and misleading. While Pacira's statements to the USPTO that the 200-liter process had "a target concentration of

bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL" were factually accurate in isolation, they were similarly incomplete and misleading in context, because Pacira never called the Examiner's attention to the fact that the claimed concentration of bupivacaine was the same as prior art 45-liter EXPAREL®.

409. Dr. Dai and Ms. Los's statements regarding the purportedly "higher" concentration of bupivacaine were but-for material to issuance of at least claim 1 of the '495 Patent. Dr. Dai successfully argued to the Examiner that the "higher" concentration of bupivacaine was a basis for allowance of claim 1, relying on Ms. Los's declaration, and incorporated the related limitation into Claim 1 to overcome the Examiner's obviousness rejection. *Supra* Section I.C.2. Indeed, in his Reasons for Allowance, the Examiner specifically noted that the Los Declaration "attest[ed] that . . . the combined art does not teach the claimed concentration of bupivacaine." JTX-4001.2311.

d. Pacira's False and Misleading Statements Were *Per Se* Material as Egregious Affirmative Misconduct

410. In addition to being but-for material as a factual matter, Pacira's false and misleading statements regarding the purported unavailability of one-month data, the purportedly "improved stability" of the 200-liter product, and the purportedly "higher" concentration of bupivacaine were *per se* material as acts of egregious affirmative misconduct.

411. Making false statements to the USPTO to obtain allowance of a claim is an egregious violation of the duty of candor. Tr. 648:24-650:7 (Slifer). Making intentionally misleading or incomplete statements to the USPTO to obtain allowance of a claim is similarly egregious, even if the statements are factually accurate if taken out of context. *Id.*

412. As discussed above, Pacira's false statement in the specification that one-month data for the reference samples did not exist ("n/a" in Table 1A) directly and affirmatively concealed the existence of the anticipatory data in the Los Spreadsheet and the Ardekani Data. *Supra* Section III.C.1.c, Section III.C.2.a.(1). As discussed below, Dr. Dai drafted Table 1A, and Ms. Los was involved in the underlying analysis and reviewed the specification during prosecution. *Infra* Section III.D.2. Both Dr. Dai and Ms. Los were in possession of the Los Spreadsheet, which indicated that some of the 45-liter reference samples underlying Table 1A had "about 23 μg/mL or less" of erucic acid after one month at 25 °C. *Infra* Section III.D.2.a.(3), Section III.D.2.b.(2). Both were aware that claim 1 of the pending claims was directed to compositions with the one-month erucic acid limitation, and explicitly distinguished the prior art on that basis. *Supra* Section I.C.2; *infra* Section III.D.2.a.(4), Section III.D.2.b.(4). In this context, Pacira's use of "n/a" in Table 1A was an affirmative act of egregious prosecution misconduct, and was therefore *per se* material.

413. As discussed above, Pacira's false and misleading statements regarding purportedly "improved stability" were a foundational basis for obtaining allowance of the '495 Patent and distinguishing the claimed product from the prior art 45-liter EXPAREL®. *Supra* Section I.C.2. Indeed, Dr. Dai and Ms. Los submitted their statements during prosecution in direct response to the Examiner's rejection, and used them to argue for the novelty of the claims based on the one-month erucic acid limitation. *Id.* As explained above, these statements regarding "improved stability" were factually false, as shown by the undisclosed information in the possession of Dr. Dai and Ms. Los. *Supra* Section III.B. In this context, Pacira's submission of false and misleading statements to the USPTO touting the purportedly "improved stability" of the claimed product was an affirmative act of egregious prosecution misconduct, and was therefore *per se* material.

414. As discussed above, Pacira's false and misleading representations regarding purportedly "higher" concentrations of bupivacaine in the 200-liter product were a foundational basis for obtaining allowance of the '495 Patent and distinguishing the claimed product from prior art. *Supra* Section I.C.2. Indeed, Dr. Dai and Ms. Los submitted their statements during prosecution in direct response to the Examiner's rejection, and used them to argue for the novelty of the claims based on the bupivacaine concentration, going so far as to add a limitation to Claim 1 directed to the bupivacaine concentration in order to obtain allowance. *Id.* These

statements regarding "higher" bupivacaine concentration were factually false, as Dr. Dai and Ms. Los were aware. *Supra* Section III.B, Section III.C.1.a-b; *infra* Section III.D.2.a.(4), Section III.D.2.b.(4). In this context, Pacira's submission of false and misleading statements to the USPTO touting the purportedly "higher" concentrations of bupivacaine in the claimed product was an affirmative act of egregious prosecution misconduct, and was therefore *per se* material.

D. INTENT TO DECEIVE DURING PROSECUTION

1. Motivation for Pacira's Deceptive Conduct

415. Mr. Molloy was Pacira's in-house counsel overseeing prosecution of the '495 Patent, and testified at trial as to Pacira's motivation for obtaining the '495 Patent. Pacira filed the application for the '495 Patent in January 2021. JTX-4121.1. At that time, almost all of Pacira's revenue came from a single product, EXPAREL®—but Pacira's only remaining Orange Book patent on EXPAREL® was about to expire, in December 2021. Unless Pacira could convince the USPTO to issue a new patent covering a purportedly "novel" form of EXPAREL® that could be listed in the Orange Book, it could face generic competition on its most important product as soon as its last Orange Book patent expired. Given these circumstances, Pacira's agents had a clear motive to do whatever was necessary to quickly obtain (and list) a new patent relevant to EXPAREL®—including deceiving the USPTO.

416. As of January 2021, Mr. Molloy was the Chief Legal and Compliance Officer at Pacira—the head of the legal department, a senior executive, and part of the leadership and management teams. Tr. 328:10-22 (Molloy). Mr. Molloy has been overseeing Pacira's intellectual property portfolio since 2015, and is involved with setting Pacira's strategy with respect to its intellectual property portfolio. Tr. 329:17-21, 334:5-14 (Molloy).

417. Mr. Molloy's oversight of Pacira's patent portfolio includes authorizing outside counsel to prosecute Pacira's patents and coordinating the interactions between inventors and prosecution counsel. Tr. 334:20-335:25 (Molloy). He is generally aware when conversations between inventors and prosecution counsel take place, and is copied on a majority of the communications between prosecution counsel and inventors. *Id.*

418. Mr. Molloy is an attorney. Tr. 328:23-24 (Molloy). Mr. Molloy is familiar with patent prosecution; he studied for and passed the patent bar, and has been a registered patent attorney since 2012. Tr. 330:8-23 (Molloy).

419. Mr. Molloy understands that attorneys and inventors have a duty of candor to the USPTO during prosecution, including disclosure of material information and the duty to be honest with the patent office. Tr. 331:11-23 (Molloy). During prosecution of the '495 Patent, Mr. Molloy understood that the duty of candor required disclosure of material prior art, including commercially sold

products prior to January 22, 2021. Tr. 332:5-20 (Molloy). He also understood that Pacira could disclose its internal data to the USPTO during prosecution. Tr. 333:3-8 (Molloy).

420. Mr. Molloy confirmed that Pacira's inventors are taught about their ethical duties during prosecution and are made aware of their duty of candor, including explicit discussion of the requirements of the duty of candor and training on required disclosures to the USPTO. Tr. 333:9-334:1 (Molloy).

421. Mr. Molloy understands that it is strategically desirable for branded pharmaceutical companies such as Pacira to have patents listed in the Orange Book for their drugs. Tr. 337:18-21 (Molloy). Specifically, Mr. Molloy knows that if a pharmaceutical company has Orange Book patents, that typically allows the company to obtain a stay on FDA approval for any company that attempts to market a generic version of the drug. Tr. 336:14-337:17 (Molloy).

422. As of the end of 2020, Mr. Molloy was aware that EXPAREL was Pacira's most important product. Tr. 340:5-9 (Molloy). Specifically, in 2020, Pacira reported a total of $422.1 million in total net profit sales, of which $413.3 million came from EXPAREL (more than 95%). Tr. 340:24-341:15 (Molloy); DTX-3116.10. Today, Pacira still derives almost 85% of its sales from EXPAREL, including almost $540 million in total net profit sales in 2023. Tr. 341:16-22 (Molloy); DTX-3116.10.

423. As of the end of 2020, Pacira only had one patent listed in the Orange Book for EXPAREL (U.S. Patent 9,585,838). Tr. 339:6-19 (Molloy); DTX-2019.1262. It was set to expire on December 24th, 2021, at which point Pacira would have no more patents in the Orange Book relevant to EXPAREL®. Tr. 339:6-19 (Molloy); DTX-2019.1262. Unless Pacira was able to obtain new patents relevant to EXPAREL®, it would have no Orange Book patents left after December 24, 2021; under that scenario, a generic company could file an application seeking approval of a generic EXPAREL® product without providing notice to Pacira and the FDA could immediately approve the ANDA without a 30-month stay. Tr. 339:20-340:4 (Molloy).

424. However, Pacira could not list a new patent in the Orange Book if it was directed only to a manufacturing process. Tr. 359:10-14 (Molloy). The only way to get a new patent listed in the Orange Book was to certify that the patent purportedly covered a novel product. Tr. 359:10-14, 357:13-359:2 (Molloy); DTX-2332.3.

425. Mr. Molloy authorized prosecution of the ’495 Patent and Pacira’s related patents. Tr. 341:24-342:13 (Molloy). He was the only in-house contact at Pacira for Dr. Dai, Pacira’s relationship partner at Knobbe Martens. Tr. 342:19-343:1 (Molloy). Mr. Molloy had many communications with Dr. Dai about

prosecution of the ’495 Patent and received copies of all filings during prosecution, as well as some drafts. Tr. 343:16-344:6 (Molloy).

426. After the ’495 Patent issued, Pacira immediately announced its issuance to the investing public, because the patent was so important to the company’s financial position that it was a “material event” requiring disclosure. Tr. 355:15-357:9 (Molloy); DTX-2078.2.

2. At Least Jane Dai and Kathleen Los Engaged in Prosecution Misconduct with the Intent to Deceive the USPTO

427. Dr. Jane Dai was the lead prosecuting attorney for the ’495 Patent; Ms. Kathleen Los was the lead inventor coordinating with Dr. Dai. *Infra* Section III.C.3.2.a(1), Section III.C.3.2.b.(1). Dr. Dai and Ms. Los were substantively involved in prosecution of the ’495 Patent, and had a duty of candor to the USPTO during prosecution. *Id.*; Tr. 620-23-621:17 (Slifer); Tr. 844:11-17 (Godici); DTX-2200.2. Both were aware of their duty of candor to the USPTO during prosecution. *Infra* Section III.C.3.2.a(1), Section III.C.3.2.b.(1). Despite their awareness of their ethical duties, Dr. Dai and Ms. Los consistently and systematically failed to comply with them—they affirmatively concealed highly material information during prosecution, and affirmatively made false and misleading statements to the Examiner regarding the prior art that would have been contradicted by the information that they concealed. *Infra* Section III.D.2.a-b.

428. The single most reasonable inference based on the evidence is that at least Dr. Dai, and Ms. Los knowingly and intentionally withheld material information from the USPTO and/or provided affirmative false and misleading statements to the USPTO with the intent to deceive, as described herein for each individual. The withheld information and affirmative false and misleading statements were but-for material to the issuance of one or more claims in the '495 Patent and constituted egregious misconduct.

a. Dr. Dai Withheld Material Information and Made False and Misleading Statements with the Intent to Deceive the USPTO

429. As explained below, Dr. Dai is an experienced patent prosecutor, with full knowledge of her ethical duties to the USPTO during prosecution. During prosecution of the '495 Patent, Dr. Dai received and reviewed the anticipatory data in the Los Spreadsheet, but intentionally withheld that data from the USPTO—and concealed the one-month data through her use of "n/a" in Table 1A. She repeatedly made false and misleading statements to the USPTO during prosecution regarding purportedly "improved stability" and "higher" bupivacaine concentration of the claimed product compared to the prior art in order to obtain allowance of the claims. Neither Pacira nor Dr. Dai has offered any plausible justification for her consistent pattern of deceptive conduct during prosecution. The single most reasonable inference based on the evidence is that Dr. Dai knowingly withheld material data

and made false and misleading statements during prosecution with the intent to deceive the USPTO.

(1) Dr. Dai's Background and Role During Prosecution

430. Dr. Dai has been a registered patent agent since 2007 (which required her to pass the patent bar), became a licensed attorney in 2011, and became a registered patent attorney in 2012. JTX-4288.2-3 (Dai Tr. 23:23-24:02, 34:04-09, 35:07-35:10); DTX-2205.1. Dr. Dai has prosecuted between 200 and 500 patents over the course of her career. JTX-4288.2 (Dai Tr. 27:16-27:19). In addition to her legal credentials, Dr. Dai has a B.S. in Chemistry and a Ph.D. in Organic Chemistry, and her legal practice focuses on "clients in life sciences." DTX-2186.1-2.

431. Dr. Dai has been working with Pacira since 2012, shortly after she first became licensed as an attorney, and has prosecuted between 30 and 50 patent applications on Pacira's behalf. JTX-4288.3 (Dai Tr. 35:19-35:23, 36:20-36:22, 36:25). She testified that she does not independently search for prior art to Pacira applications, because she believes that "multivesicular liposome technology is a very special technology, [and] there's not a lot of prior art that's out there." *Id.* (Dai Tr. 46:07-10, 48:02-09).

432. Dr. Dai was the lead prosecution attorney who drafted and submitted prosecution documents to the USPTO during prosecution of the '495 Patent. Tr. 342:14-18 (Molloy); JTX-4288.4 (Dai Tr. 58:16-17, 59:1-13). During prosecution,

Dr. Dai sent copies of prosecution filings to Mr. Molloy, Ms. Los, and Dr. Ardekani, and had many communications with Mr. Molloy about prosecution of the '495 Patent. JTX-4288.5 (Dai Tr. 65:17-22, 65:24-66:3); Tr. 343:16-344:6 (Molloy).

433. Dr. Dai supervised the drafting of the application for the '495 Patent, worked on the draft with the assistance of a Knobbe associate, and reviewed the final application before it was filed. JTX-4288.4 (Dai Tr. 58:16-17, 59:1-13). Dr. Dai drafted Table 1A of the '495 Patent, and decided what to include in that Table. Tr. 343:5-16 (Molloy); JTX-4288.8 (Dai Tr. 94:19-20). However, Dr. Dai did not draft Figures 3A, 3B, or 3C of the '495 Patent, which were provided to her by Ms. Los. JTX-4288.4-5 (Dai Tr. 61:14-15, 61:22, 63:12-13).

434. Dr. Dai received a copy of the Los Spreadsheet in connection with her prosecution of the '495 Patent. JTX-4288.9-10 (Dai Tr. 110:17-111:02, 112:5-7, 112:12-14); JTX-4119.1. She reviewed the Los Spreadsheet in connection with prosecution of the '495 Patent, and the data in the Los Spreadsheet was the basis for the data tables in the '495 Patent. JTX-4288.10 (Dai Tr. 114:06-8, 114:15-21, 114:25-115:03); JTX-4037.18-19.

435. Dr. Dai understood herself to have a duty of candor to the USPTO during prosecution of the '495 Patent. JTX-4288.13 (Dai Tr. 128:10-17). She understood that her duty of candor encompassed a duty to be honest with the USPTO, including avoiding making false or misleading statements, and a duty to

disclose material prior art to the USPTO. JTX-4288.13-14 (Dai Tr. 128:23-129:9, 129:10-13, 131:13-132:22, 132:23-133:10); DTX-2200.4. Additionally, she understood that prior commercial sales of a product could constitute prior art, and that EXPAREL® had been marketed prior to the filing of the '495 Patent. JTX-4288.13-15 (Dai Tr. 129:14-16, 129:22-130:3, 133:11-25); DTX-2200.4. Dr. Dai further understood that material information needed to be disclosed to the USPTO even if it was a trade secret or proprietary information, consistent with the requirements in Chapter 700 of the MPEP. JTX-4288.16-17 (Dai Tr. 138:12-17, 139:1-4, 139:11-140:4); DTX-2201.295.

436. During prosecution, Dr. Dai understood that the MPEP defined material information to include information that "is not cumulative to information already of record . . . and . . . establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim, or . . . refutes or is inconsistent with a position the applicant takes in opposing an argument of unpatentability relied on by the office, or asserting an argument of patentability." JTX-4288.15 (Dai Tr. 134:15-135:10); DTX-2200.5. She further understood that material information included "any information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow the application to issue as a patent," consistent with the language in the MPEP. JTX-4288.15 (Dai Tr. 134:1-14); DTX-2200.4.

(2) Dr. Dai Knowingly Withheld Material Information from the USPTO

437. During prosecution of the '495 Patent, Dr. Dai was in possession of the Los Spreadsheet, indicating that at least claims 1, 3, and 5 of the '495 Patent were anticipated by prior art 45-liter EXPAREL®. *Supra* Section III.B.1. Dr. Dai withheld this information from the USPTO during prosecution of the '495 Patent. *Id.* The most reasonable inference is that Dr. Dai knew that this information was highly material, but intentionally concealed it from the Examiner during prosecution.

438. During prosecution of the '495 Patent, Dr. Dai drafted the specification and the only independent claim, claim 1, to focus on bupivacaine MVL compositions with "about 23 μg/mL or less" of erucic acid after one month of storage at 25 °C. *Supra* Section I.C.1-2. Dr. Dai understood that claim 1 of the '495 Patent was a product-by-process claim, and that for product-by-process claims, the product has to be novel compared to the prior art. JTX-4288.5 (Dai Tr. 67:10-16). During prosecution, Dr. Dai's understanding of the scope of the claims was informed by conversation with at least Ms. Los (and potentially additional inventors), who consistently testified that they understood the one-month erucic acid concentration in claim 1 as its only point of potential novelty. JTX-4288.5 (Dai Tr. 69:24-70:2, 70:5, 71:14-16, 72:22-71:25); *supra* Section III.1.4.

439. Additionally, during prosecution, Dr. Dai explicitly distinguished claim 1 from the prior art based on the one-month erucic acid limitation in claim 1 on multiple occasions. *Supra* Section I.C.2.

440. The single most reasonable inference is that Dr. Dai was aware, during prosecution, that the one-month erucic acid limitation in claim 1 was a key potential point of novelty over prior art 45-liter EXPAREL®.

441. Prior to filing the '495 Patent, Dr. Dai received and reviewed the Los Spreadsheet, and used the data in the Los Spreadsheet to draft the tables in the specification. JTX-4288.9-10 (Dai Tr. 110:17-111:02, 112:5-7, 112:12-14, 114:06-8, 114:15-21, 114:25-115:03); JTX-4119.1; JTX-4037.

442. As discussed above, the Los Spreadsheet contained erucic acid stability data at 25 °C for 45-liter batches 16-P004, 16-3088, 16-3089, and 16-3090. *Supra* Section III.B.1. This stability data indicated that batches of prior art EXPAREL® met the erucic acid limitations of the claims of the '495 Patent at the one-month timepoint (claim 1), the two-month timepoint (claim 3), and the three-month timepoint (claim 5), and therefore showed that each of these claims was anticipated. *Supra* Section III.B.C.1.a.

443. During her testimony, Dr. Dai confirmed that she was able to understand the disclosures in the Los Spreadsheet—perhaps unsurprisingly, given her scientific background and her years of experience working with Pacira and other

life sciences companies. JTX-4288.2-3 (Dai Tr. 34:4-15, 35:7-10, 35:19-23) Dr. Dai understood that the "LT 20" entries in the Los Spreadsheet meant "less than 20 µg/mL." JTX-4288.12 (Dai Tr. 120:6-12); JTX-4037.18. Based on the data in the Los Spreadsheet, Dr. Dai specifically confirmed that she was aware during prosecution that 45-liter batches 16-P004, 16-3089, and 16-3090 had less than 20 µg/mL erucic acid after storage at 25 degrees C for one month, which is less than 23 µg/mL of erucic acid. JTX-4288.12 (Dai Tr. 120:6-17, 120:20, 120:25-121:7).

444. As discussed above, Dr. Dai was aware of the MPEP's definition of materiality, and her obligation to disclose information related to prior-art EXPAREL® that established unpatentability of a claim, contradicted her other statements or arguments to the Examiner, or was otherwise information that a reasonable examiner would be likely to consider important in assessing patentability. *Supra* Section III.D.2.a.(1). The withheld data in the Los Spreadsheet fell into each of these categories. The single most reasonable inference is that Dr. Dai was aware during prosecution that the 45-liter data in the Los Spreadsheet was highly material (and indeed, anticipatory) to at least claims 1, 3, and 5 of the application for the '495 Patent.

445. Despite Dr. Dai's awareness of the highly material, anticipatory data in the Los Spreadsheet during prosecution of the '495 Patent, she never disclosed that data to the USPTO. Dr. Dai was aware that individual batch data for the 45-liter

batches in the Los Spreadsheet was never provided to the USPTO during prosecution of the '495 Patent. JTX-4288.12 (Dai Tr. 127:09-12, 127:15). At deposition, Defendants asked Dr. Dai why this data was never provided to the USPTO; she declined to answer, and did not provide any affirmative explanation for her conduct. JTX-4288.12-13 (Dai Tr. 127:16-128:1).

446. During prosecution of the '495 Patent, Dr. Dai submitted three separate Information Disclosure Statements ("IDSs") disclosing almost 300 literature references to the USPTO, but never disclosed Pacira's individual batch data for its 45-liter batches. JTX-4288.20-21 (162:6-16, 162:24-163:2, 163:5-167:10); DTX-2196.106-117, .125, .157). When Dr. Dai chose to pursue this disclosure strategy, she was aware that there was limited published art available regarding MVL technology, as compared to Pacira's internal information on the topic. JTX-4288.3 (Dai Tr. 46:07-10, 48:02-09).

447. Dr. Dai also made the affirmative decision to exclude the anticipatory data in the Los Spreadsheet when drafting Table 1A of the '495 Patent. Table 1A of the '495 Patent presents individual data for each of the 200-liter batches, but only averages for the 45-liter batches (and only at the two-, three-, and six-month timepoints):

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19 (20:49-67).

448. If Table 1A had included individual batch data for the underlying 45-liter batches (i.e., the data for each of the 45-liter batches in the Los Spreadsheet), it would have revealed that at least claims 1, 3, and 5 were anticipated by prior art EXPAREL®. *Supra* Section III.C.1a.

449. There was no scientific rationale to report full data for the 200-liter batches in Table 1A, but only averages for the 45-liter batches. Tr. 426:12-17 (Schwendeman). As Ms. Los admitted, it would have been possible to report individual batch data for the 45-liter batches as well as the 200-liter batches. JTX-4289.26 (Los Tr. 129:17-19, 129:23).

450. The single most reasonable inference is that Dr. Dai intentionally drafted Table 1A of the '495 Patent to exclude the anticipatory data from the Los Spreadsheet, to conceal this information from the USPTO.

451. Dr. Klibanov testified that in his opinion, the omission of individual batch data from Table 1A was consistent with scientific practice because "averages are often used in scientific literature when the number of individual data points is substantial. For example, usually exceeds 3 to 5." Tr. 754:10-22 (Klibanov). This excuse is not plausible. The Los Spreadsheet itself presents individual batch data for all of the 45-liter batches as well as all of the 200-liter batches. JTX-4037.18. The 45-liter data in the Los Spreadsheet was not voluminous—it included only ten 45-liter batches, and only seven were used to calculate the values in Table 1A. *Supra* Section III.B.1. It is simply not credible that Dr. Dai affirmatively chose to omit the 45-liter batch data from Table 1A to save space, given the materiality of that data and the small number of samples involved.

452. This purported explanation is additionally implausible in view of the other data in the Los Spreadsheet, and Dr. Dai's drafting decisions for the other data tables in the '495 Patent. The Los Spreadsheet contained internal pH and internal lysine data for only two 45-liter batches—lots 19-3079 and 19-3091. JTX-4289.30-31 (Los Tr. 146:01-10); JTX-4037.28, 45-46. Despite this, the internal pH and lysine data tables in the '495 Patent show individual batch data for all three 200-liter

batches, but only an average for the 45-liter batches—even though there were ***fewer*** 45-liter batches analyzed than 200-liter batches. JTX-4121.20 (Tables 2A and 2B). The single most reasonable inference is that Dr. Dai consistently omitted individual batch data from the tables in the '495 Patent to conceal Pacira's underlying data on its 45-liter batches.

453. Rather than disclose the anticipatory data in the Los Spreadsheet to the USPTO during prosecution, Dr. Dai (1) told the USPTO that the anticipatory one-month data did not exist (*supra* Section III.C.2.a.(1); *infra* Section III.D.2.a.(3)) and (2) repeatedly represented to the Examiner that the claimed product had "improved stability" compared to prior art EXPAREL®. *Supra* Section I.C.2; *infra* Section III.D.2.a.(4)..

454. The single most reasonable inference from the evidence is that Dr. Dai was aware during prosecution that the 45-liter data in the Los Spreadsheet was highly material (and indeed, anticipatory) to at least claims 1, 3, and 5, but intentionally chose to withhold this data from the USPTO.

455. As discussed above, Plaintiffs now argue that the one-month data in the Los Spreadsheet for the 45-liter batches was cumulative of disclosures in Figure 3B of the specification. *Supra* Section III.C.1.c. For at least the reasons above, this argument is incorrect, and would not excuse Dr. Dai's withholding of the material data in the Los Spreadsheet even if true. *Supra* Section III.1.A. To the extent that

Plaintiffs argue that Dr. Dai may have withheld the data in the Los Spreadsheet from the USPTO based on an erroneous determination that it was cumulative (rather than out of an intent to deceive), there is no support for that argument in the record. Such an inference would not be plausible in view of the evidence.

456. First, Dr. Dai did not provide any affirmative explanation as to why she withheld the 45-liter batch data in the Los Spreadsheet from the USPTO during prosecution of the '495 Patent, including whether she made any determination as to whether or not the 45-liter batch data in the Los Spreadsheet was cumulative of other information provided to the USPTO. JTX-4288.12-13, 17 (Dai Tr. 127:16-128:1, 141:21-142:7). Plaintiffs asserted privilege over whether Dr. Dai withheld the 45-liter data in the Los Spreadsheet based on any assessment of cumulativeness, and cannot excuse Dr. Dai's conduct by speculating on her hypothetical assessment of cumulativeness after refusing to provide discovery on that topic. *Id.*

457. Second, there is no contemporaneous evidence from the time of prosecution supporting the idea that Dr. Dai withheld the material data in the Los Spreadsheet based on "cumulativeness," or as otherwise non-material. The MPEP recommends that "if information was specifically considered and discarded as not material, this fact might be recorded in an attorney's file . . . including the reason for discarding it," as "a note made at the time of evaluation might be an invaluable aid in explaining that" that any potential error in disclosure "was honest and excusable."

DTX-2200.13. During prosecution, Dai did not make any such note with respect to the 45-liter batch data in the Los Spreadsheet. JTX-4288.15-16 (Dai Tr. 136:17-137:14, 138:2).

458. During Dr. Dai's deposition, Pacira's attorneys elicited testimony about the purported disclosures of Figure 3B. JTX-4288.24-26 (Dai Tr. 248:13-250:23, 251:5-7, 251:9-13). However, there is no evidence that Dr. Dai interpreted Figure 3B in this way during prosecution of the '495 Patent, or that Figure 3B was a factor in her decision to withhold data from the USPTO. Dr. Dai did not draft Figure 3B. JTX-4288.4-5 (Dai Tr. 61:14-15, 61:22, 63:12-13). She never discussed Figure 3B with the Examiner during prosecution. JTX-4288.29 (Dai Tr. 255:22-23, 256:04)). She did not testify that Figure 3B influenced her decision to withhold Pacira's data from the USPTO during prosecution—indeed, Dr. Dai was asked why she withheld this data and whether she made any determination of cumulativeness, and she declined to respond. JTX-4288.12-13, 17 (Dai Tr. 127:16-128:1, 141:21-142:7). Moreover, when Dr. Dai was asked to confirm that Figure 3B did not depict measured data points at the one-month timepoint, she became evasive and refused to answer. JTX-4288.27-28 (Dai Tr. 253:14-16, 253:18-255:5); JTX-4121.8.

459. As discussed above, the testimony of Ms. Los—who did draft Figure 3B, and was in communication with Dr. Dai throughout prosecution—is inconsistent with the idea that Ms. Los intended for Figure 3B to disclose extrapolated one-month

averages for the 45-liter batches. *Supra* Section III.C.1.c. Notably, Pacira chose not to elicit any testimony from Ms. Los about the interpretation of Figure 3B at her deposition, despite the fact that Ms. Los did draft Figure 3B. JTX-4288.4-5 (Dai Tr. 61:14-15, 61:22, 63:12-13); JTX-4289.30 (Los Tr. 144:15-144:24, 145:06-10); JTX-4037.20-21.

460. Additionally, Dr. Dai's prosecution conduct is inconsistent with the idea that she could have believed Figure 3B to disclose an extrapolated one-month average for the 45-liter batches. As discussed above, Dr. Dai explicitly and repeatedly represented to the USPTO that the one-month erucic acid limitation was a point of novelty over the prior art. *Supra* Section I.C.2. Relying on the one-month erucic acid limitation as a purported point of novelty would not make sense if Dr. Dai believed that the Examiner was aware that prior art EXPAREL® already met this limitation.

461. Further, as discussed above, even if the one-month data in the Los Spreadsheet was cumulative over Figure 3B (which it was not), the Los Spreadsheet clearly contained a "more complete combination of relevant features" with respect to erucic acid and external pH over time for the 45-liter batches than appeared in the specification, which was highly material to the patentability of at least claims 2-6. DTX-2200.11 (MPEP Chapter 2200); *supra* ¶ 353. Even if there were any evidence to support the inference that Dr. Dai considered the one-month data in the Los

Spreadsheet to be "cumulative" of Figure 3B (which there is not), there is no evidence to support the idea that she could have plausibly reached the conclusion that the Los Spreadsheet failed to contain highly material information requiring disclosure.

462. Dr. Dai's conduct in prosecuting subsequent Pacira applications also belies the idea that she believed Figure 3B to disclose a one-month average lower than "about 23 μg/mL" for erucic acid in prior art 45-liter EXPAREL®. As discussed in more detail below, Dr. Dai selectively added a footnote to Table 1A in certain Pacira applications after receiving Jiangsu Hengrui's Notice Letter, explaining the meaning of "n/a" and disclosing that some 45-liter batches of EXPAREL® met the one-month erucic acid limitation; however, this disclosure came only in the applications with no one-month erucic acid limitation, and only after all patents with a one-month erucic acid limitation had already issued. *Infra* Section III.D.3.a. The only plausible explanation for this pattern of conduct is that Dr. Dai knew that the Pacira's withheld data for 45-liter EXPAREL® showed that some batches anticipated the one-month erucic acid claims, and that once she disclosed that fact to the USPTO, she would be unable to obtain further claims to the one-month timepoint. If Dr. Dai believed that the USPTO already knew about the existence of these batches through Figure 3B, there would be no need to selectively omit the footnote under Table 1A from all patents with one-month erucic acid

limitations, or to stop pursuing new claims with the one-month limitation after adding the footnote.

(3) Dr. Dai Knowingly Made False Statements to Conceal Pacira's Anticipatory One-Month Data

463. As discussed above, Table 1A of the '495 Patent falsely states that the one-month average for the reference samples is "n/a"—i.e., that no data existed at the one-month timepoint. *Supra* Section III.C.2.a.(1). In reality, this one-month data was in Dr. Dai's possession in the Los Spreadsheet, and indicated that claim 1 was anticipated (as well as at least dependent claims 3 and 5). *Supra* Section III.B.1.

464. Dr. Dai supervised the drafting of Table 1A, including the decision to report "n/a" in Table 1A at the one-month timepoint for the 45-liter reference samples. JTX-4288.9 (Dai Tr. 98:01-3, 98:6-7). Dr. Dai agreed that she provided no numerical values for one-month data of the reference samples in Table 1A, despite the fact that one-month data did in fact exist for those reference samples. JTX-4288.9 (Dai Tr. 96:04-11, 98:18-23, 99:02).

465. Dr. Dai initially testified that she understood "n/a" to typically mean "not applicable," but later admitted that she understood the "NA" entries in the Los Spreadsheet to mean "not available." JTX-4288.9, 11-12 (Dai Tr. 98:8-12, 119:25-120:5); JTX-4037.18.

466. For at least the reasons discussed above, Pacira's purported excuses for the use of "n/a" in Table 1A are not plausible. *Supra* Section III.C.2.a.(2).

467. Additionally, as discussed above, Dr. Dai's conduct during prosecution of the '495 Patent and subsequent related patents shows her knowledge that the existence of 45-liter batches meeting the one-month erucic acid limitation had never been disclosed to the Examiner, and was a key point of purported novelty over the prior art. *Supra* Section III.D.2.a.(2).

468. The single most reasonable inference is that Dr. Dai was aware that her use of "n/a" in Table 1A was a false and misleading statement in view of the undisclosed, anticipatory one-month data in the Los Spreadsheet.

(4) Dr. Dai Knowingly Made False Statements Regarding "Improved Stability" and "Higher" Bupivacaine Concentration

469. As discussed above, Dr. Dai repeatedly represented to the Examiner in the specification and during prosecution that the claimed product had "improved stability" and "higher" concentration of bupivacaine than prior-art EXPAREL®. *Supra* Section I.C.2. These false and misleading representations were instrumental in obtaining allowance of the '495 Patent. *Id.* For at least the reasons below, the single most reasonable inference is that Dr. Dai was aware that these statements were false and misleading when she made these representations to the USPTO.

470. Dr. Dai supervised the drafting of the specification of the '495 Patent, including its statements regarding purportedly "improved stability." JTX-4288.4 (Dai Tr. 58:16-17, 59:1-13). Although Dr. Dai initially argued that the reference to

"lower lipid hydrolysis by-products" "refers to the stability over six months measured," she admitted that this paragraph in the specification contains no language referencing the six-month timepoint. JTX-4288.6-7 (Dai Tr. 88:09-10, 88:11-12, 88:16, 88:23-89:12, 89:15-16, 89:17-19, 89:22-23); JTX-4121.16 (13:48-49). Dr. Dai understood that claim 1 of the '495 Patent had a limitation relating to the one-month erucic acid concentration, not the six-month concentration. JTX-4288.7 (Dai Tr. 89:24-90:1, 90:11-14).

471. Dr. Dai supervised the drafting of the April 22, 2021 Amendment and Response to Nonfinal Office Action, and reviewed it before signing her name to it. JTX-4288.18 (Dai Tr. 153:3-5, 153:6-154:5); DTX-2196.158, 165.

472. During prosecution, Dr. Dai submitted the Applicant Response stating that the "new commercial process yields a bupivacaine MVL product with superior stability as compared to the product made by the prior process," in the context of a paragraph arguing that the prior art identified by the Examiner did not teach an erucic acid concentration of "about 23 µg/mL or less after the composition is stored at 25 °C for one month." JTX-4288.19-20 (Dai Tr. 158:13-159:3, 160:3-161:3); DTX-2196.164. When Dr. Dai wrote that language, she had already reviewed the Los Spreadsheet, which indicated that several 45-liter batches of EXPAREL® had less than 20 µg/mL erucic acid at the one-month timepoint. JTX-4288.19-20 (Dai Tr. 158:13-159:3, 160:3-161:3); DTX-2196.164.

473. As discussed above, Dr. Dai made her statements regarding "improved stability" primarily in the context of arguing for the patentability of independent claim 1, requiring less than about 23 µg/mL erucic acid at the one-month timepoint. *Supra* Section I.C.2. In context, the single most reasonable inference is that Dr. Dai intended her statements regarding "improved stability" to give the Examiner the impression that the one-month erucic acid limitation was novel, as well as the subsequent timepoints in claims 3, 5, and 7.

474. However, Dr. Dai was in possession of the Los Spreadsheet, which clearly indicated that the one-month erucic acid limitation was not novel (as well as the two- and three-month limitations). *Supra* Section III.B.1.

475. To the extent that Plaintiffs argue that Dr. Dai may have understood her statements to be true under some unconventional definition of "improved stability," Dr. Dai testified that during prosecution, she did not have an "independent understanding" as to whether the manufacturing process disclosed in the patent yielded a more stabilized form of bupivacaine encapsulated MVLs, "beyond what was provided to [her] as privileged." JTX-4288.5-6 (Dai Tr. 86:12-16, 86:18-20). She further testified that she had no "personal understanding" of whether there was any practical significance to the erucic acid concentration differences reported in the '495 Patent, "independent of the privileged information [she] received." JTX-4288.9 (Dai Tr. 108:18-21, 109:8-10).

476. As discussed above, there was no factual basis during prosecution for any reasonable person to conclude that the 200-liter process had "improved stability" compared to the 45-liter process, particularly not a difference that would be of practical significance. Section II.B.2, Section II.C.2. Additionally, as discussed below, the single most reasonable inference from the evidence is that Ms. Los was aware that the 200-liter product did not have "improved stability" over the 45-liter product. *Infra* Section III.D.2.b.(4). As such, there is no plausible basis for Plaintiffs to argue that Dr. Dai may have thought that her statements regarding "improved stability" were accurate.

477. Dr. Dai also overcame the Examiner's rejection of the '495 Patent by arguing that the claimed process resulted in a "higher concentration of bupivacaine" than the prior art, and amending the claims accordingly. *Supra* Section I.C.2. These statements were false, misleading, and/or misleadingly incomplete—EXPAREL® manufactured using the 200-liter process has an identical concentration of bupivacaine to prior art 45-liter EXPAREL®, which Dr. Dai did not mention to the Examiner in making her argument of novelty. *Supra* Section III.C.2.c. There is no plausible factual basis for which Dr. Dai could have believed her representations of "higher concentrations" of bupivacaine; indeed, Ms. Los, who authored the Los Declaration in support of this argument, knew that there was no difference in

bupivacaine concentration between the 200-liter product and prior art EXPAREL®. JTX-4289.46 (Los Tr. 212:13-16).

478. As such, the single most reasonable inference is that Dr. Dai knew that her statements to the Examiner regarding a purportedly "higher concentration" of bupivacaine were false and misleading.

(5) The Single Most Reasonable Inference Is that Dr. Dai Acted with the Intent to Deceive the USPTO

479. The single most reasonable inference is that Dr. Dai knowingly withheld material information from the USPTO during prosecution and knowingly and repeatedly made false statements to the Examiner with the intent to deceive the USPTO. Each of Dr. Dai's instances of misconduct went directly to key issues during prosecution, and were instrumental in obtaining issuance of the '495 Patent. *Supra* Section I.C.2. Standing alone, each instance would be an egregious violation of the duty of candor, and the single most reasonable inference for each instance of misconduct is that Dr. Dai intended to deceive the USPTO. As a whole, Dr. Dai's pattern of conduct is even more egregious, showing a sustained pattern of targeted deception calculated to mislead the Examiner into allowing the claims of the '495 Patent.

480. Dr. Dai had worked with Pacira for years before she filed the application for the '495 Patent. *Supra* Section III.D.2.a.(1). She communicated

regularly with Mr. Molloy regarding prosecution of the '495 Patent. *Id.* In view of these conversations, Dr. Dai filed the '495 Patent on January 22, 2021, and requested prioritized examination—which would allow the patent to issue within approximately twelve months, rather than a longer period of time. *Supra* Section III.A.1. The single most reasonable inference is that Dr. Dai was well aware when she filed the '495 Patent that Pacira desperately needed a new product patent that could be listed in the Orange Book before its old patents expired in December 2021—i.e., a patent purportedly directed to a new product, rather than merely a new manufacturing process. *See supra* Section III.D.1.

481. When prosecuting the '495 Patent, the single most reasonable inference is that Dr. Dai knew that she had material information in her possession (the Los Spreadsheet) that showed anticipation of at least claims 1, 3, and 5 of the pending application. *Supra* Section III.B.1, Section III.C.1.a. She was fully aware of this data and its relevance to the patent—indeed, the Los Spreadsheet was the basis for the data reported in the sections of the patent that she drafted. *Supra* Section III.B.1.

482. Dr. Dai was aware that the one-month erucic acid limitation was essential for showing novelty of the only independent claim, claim 1. *Supra* Section I.C.2. She was also aware that multiple batches of prior art 45-liter EXPAREL® fell within the one-month limitation, and therefore anticipated claim 1 (as well as at least dependent claims 3 and 5). *Supra* Section III.B.1, Section III.C.1.a.

483. Rather than disclose this but-for material information to the Examiner, Dr. Dai affirmatively concealed it. She intentionally drafted Table 1A to falsely state that one-month data did not exist for the 45-liter batches, excluding the individual 45-liter batch data and reporting only averages so that the Examiner would not see the anticipatory batch data (while reporting individual values for the 200-liter batches, which would not threaten her ability to get a patent allowed). Section III.C.2.a.(1). Additionally, she included multiple statements in the specification regarding purportedly "improved stability," to give the impression that Pacira's data showed a meaningful difference in stability at all claimed timepoints (1, 2, 3, and 6 months)—despite knowing that Pacira's data showed no such difference. *Supra* Section III.C.2.b.(1).

484. Dr. Dai's selective addition of a footnote explaining the "n/a" in Table 1A to some of Pacira's related patents—though not to any of the patents with the one-month erucic acid limitation—further confirms her awareness that Table 1A concealed the existence of anticipatory data, as originally drafted. *Infra* ¶ 571. Dr. Dai's ongoing pattern of concealing this data from the USPTO for all patents where it would impact her ability to obtain allowance of one-month claims confirms that her concealment of this data was knowing, intentional, carefully planned, and designed to mislead the USPTO. *Id.*

b. Ms. Los Withheld Material Information and Made False and Misleading Statements with the Intent to Deceive the USPTO

485. As explained in further detail below, Ms. Los was the lead inventor coordinating with prosecution counsel Dr. Dai during prosecution of the '495 Patent. She drafted the Los Spreadsheet, and assisted in analyzing its data for the purpose of drafting the '495 Patent. Specifically, Ms. Los compiled the data in the Los Spreadsheet based on a larger set of data, the Ardekani Data. However, Ms. Los excluded key information from the Ardekani Data in drafting the Los Spreadsheet—the eight Swindon batches in the Ardekani Data that showed anticipation of claim 7, with the six-month erucic acid limitation, as well as claims 1, 3, and 5 at earlier timepoints. During prosecution, Ms. Los also submitted the Los Declaration to the USPTO attesting to the purportedly "superior stability" of the 200-liter product and implying that it had a "higher concentration" of bupivacaine compared to the prior art, while knowing these representations to be false. The single most reasonable inference based on the evidence is that Ms. Los knowingly withheld material data and made false and misleading statements during prosecution with the intent to deceive the USPTO.

(1) Ms. Los's Background and Role During Prosecution

486. As of the date of her deposition testimony, Ms. Los had the title of "Director of Formulation Development at Pacira." JTX-4289.4 (Los Tr. 35:11-13).

However, Ms. Los reported directly to Elena McDermott, an attorney on Pacira's internal legal team with responsibility for this litigation. JTX-4289.4 (Los Tr. 35:14-24, 36:01-5).

487. Ms. Los has not done any bench science since approximately 2019 or 2020. JTX-4289.4 (Los Tr. 36:6-9, 36:11-16). Instead, her current job duties include "participat[ing] in developing patent strategies and writing patent documents," including "provid[ing] data to support the drafting of patents." JTX-4289.4-5 (Los Tr. 36:17-21, 36:24-37:4, 37:15-22). Over the past few years, 50-60% of Ms. Los's work has related to patent matters. JTX-4289.6 (Los Tr. 47:03-6, 47:8).

488. Ms. Los has been working with Jane Dai for approximately five to ten years on patent strategies and drafting patent documents, as well as with Elena McDermott and Anthony Molloy as in-house counsel at Pacira. JTX-4289.5-6 (Los Tr. 44:13-15, 44:20-45:1, 45:12-14, 45:20-24, 46:1, 46:3).

489. Ms. Los has been involved with work related to EXPAREL on and off for approximately the past twenty years, but had no role in the 200-liter scale-up of the EXPAREL® manufacturing process. JTX-4289.8 (Los Tr. 50:19-51:4, 51:6-9, 51:11-15). She was aware of stability testing being performed over the years on EXPAREL® by Pacira's quality control group, and some of her responsibilities

required her to review stability testing results for EXPAREL®. JTX-4289.8-9 (Los Tr. 51:16-24, 52:5-7).

490. Ms. Los is aware that EXPAREL® is Pacira's top-selling product. JTX-4289:7 (Los Tr. 49:10-16). She is aware that Orange Book patents protect a brand-name company from generic competition, and that it is desirable for a drug company to have more Orange Book patents, rather than fewer. JTX-4289.11 (Los Tr. 64:2-4, 64:22-24, 65:02-8, 65:14). Ms. Los is aware that the '495 Patent is now listed in the Orange Book. JTX-4289.11 (Los Tr. 63:1-4).

491. As of 2020, Ms. Los was aware that Pacira had Orange Book patents listed for EXPAREL, but that those patents would expire at the end of 2021, which would be unfavorable for Pacira. JTX-4289:11-12 (Los Tr. 65:15-23, 65:25-66:6, 66:16-18). Ms. Los understood that the launch of a generic product would have had a negative impact on Pacira's finances. JTX-4289.64 (Los Tr. 273:16-18, 273:21-22).

492. During prosecution, Ms. Los was aware that she had a duty of candor to the patent office. JTX-4289.41 (Los Tr. 190:7-9, 190:11-13, 190:20-21). She understood that this duty of candor required her to disclose "data that was relevant to what the patent was about" and to provide any documents or data of potential importance to her attorneys. JTX-4289.41-42 (Los Tr. 190:22-191:2, 192:15-20, 192:22). Additionally, she understood that she had a duty to be honest with the

USPTO, and that the duty of candor "of course include[d] not intentionally misleading the patent office." JTX-4289.41, 43 (Los Tr. 191:3-5, 193:16-18, 193:21-24).

493. With respect to prosecution of the '495 Patent, Ms. Los compiled the comparative data underlying the '495 Patent—i.e., the data in the Los Spreadsheet, which she provided to Dr. Dai in connection with prosecution. *Supra* ¶ 304. Ms. Los also drafted the figures of the '495 Patent, including Figure 3B, and assisted with the mathematical analysis in Table 1A. JTX-4289.22-23, 30 (Los Tr. 122:16-22, 124:2-12, 144:15-24, 145:6-10); JTX-4037.20-21; JTX-4288.4-5 (Dai Tr. 61:14-15, 61:22, 63:12-13). She received updates from Dr. Dai throughout prosecution with copies of prosecution filings. JTX-4288.5 (Dai Tr. 65:17-22, 65:24-66:3). Additionally, Ms. Los submitted a Declaration during prosecution in support of Dr. Dai's arguments to overcome the Examiner's obviousness rejection. *Supra* Section I.C.2.

(2) Ms. Los Assisted Dr. Dai in Concealing the Anticipatory Data in the Los Spreadsheet from the USPTO

494. Ms. Los was familiar with the data in the Los Spreadsheet during prosecution—she compiled the Los Spreadsheet, and assisted with the mathematical analysis of the data (including the erucic acid data in Table 1A). *Supra* Section III.B.1, Section III.D.2.b.(1). As discussed above, the data in the Los Spreadsheet

showed that at least claims 1, 3, and 5 were anticipated by prior art EXPAREL®. *Supra* Section III.B.1.

495. Ms. Los confirmed that as of the filing of the patent, she was aware of 45-liter batches of EXPAREL® with concentrations of erucic acid of less than 20 µg/mL at the one-month time point. JTX-4289.39 (Los Tr. 169:20-23, 170:1-2). For instance, Ms. Los understood that the "LT 20" entries in the Los Spreadsheet for lots 16-P004, 16-3089, and 16-3090 at the one-month timepoint indicated a value of less than 20 µg/mL of erucic acid. JTX-4289.24 (Los Tr. 125:19-126:2); JTX-4037.18.

496. Ms. Los understood that the claims of the '495 Patent required specific erucic acid concentrations at specific timepoints. With respect to claim 1, Ms. Los understood that claim 1 of the '495 Patent contains processing steps in addition to two limitations directed to the "actual composition"—specifically, the "drug[] content and the erucic acid content"—and understood that the "more specific composition piece of the claim is the last sentence about erucic acid," i.e., the one-month erucic acid limitation. JTX-4289.15 (Los Tr. 79:13-14, 79:20-80:5, 80:9-11); JTX-4121.21. During prosecution, Ms. Los also submitted a Declaration explicitly arguing for the novelty of the claims on the basis of the one-month erucic acid limitation, confirming Ms. Los's knowledge that this limitation was key to patentability. *Supra* Section I.C.2.

497. Ms. Los understood that Pacira's historical data showing that certain 45-liter batches met the erucic acid limitation of claim 1 was relevant to patentability, and that it needed to be disclosed to the USPTO. When shown Pacira's older historical data indicating a one-month average lower than 23 µg/mL for certain 45-liter batches, Ms. Los stated that this data "d[id] seem relevant" to the one-month limitation in the '495 Patent, and that this was the type of information that she would have disclosed to the patent office if she had considered it. JTX-4289.62 (Los Tr. 268:2-7, 268:11-14, 268:22).

498. During prosecution of the '495 Patent, Ms. Los was aware that no data on individual batches of 45-liter EXPAREL had been provided to the USPTO. JTX-4289.43 (Los Tr. 197:25-198:3, 198:9).

499. Ms. Los was also aware that Table 1A had been constructed so as to conceal the individual batch data for the 45-liter batches, and that it falsely stated that one-month data for the 45-liter batches did not exist.

500. Ms. Los understood that Table 1A shows individual batch data for Batches 1, 2, and 3 (i.e., the 200-liter batches), and no individual batch data for the "reference samples" prepared by the "current commercial process" (i.e., the 45-liter batches). JTX-4289:16-17 (Los Tr. 81:10-81:22, 81:24-82:5, 82:7-14); JTX-4121.19. She also understood that Table 1A of the '495 Patent lists one-month data for the 200-liter batches, but only "n/a" for the one-month average of the 45-liter

reference samples. JTX-4289.17 (Los Tr. 82:22-83:5, 85:5-7). Ms. Los confirmed that to her understanding, there is no further explanation in the specification as to what "n/a" means in Table 1A. JTX-4289.17 (Los Tr. 85:14-16, 85:18).

501. Ms. Los initially testified that to her understanding, "n/a" generally stands for "not applicable." JTX-4289.17 (Los Tr. 85:8-10). However, she later admitted that in the Los Spreadsheet, she used the abbreviation "NA" at the six-month timepoint for batches 20-3066, 20-3067, and 20-4076 to mean "no data available." JTX-4289.23 (Los Tr. 124:11-22, 124:24); JTX-4037.18. When confronted with her own use of "NA" to mean "not available," Ms. Los agreed that the "n/a" in Table 1A could be read as a statement that data was not available at the one-month timepoint. JTX-4289.39-40 (Los Tr. 171:3-4, 171:7-10, 172:11-14, 172:16-18, 172:19-25, 173:02).

502. Ms. Los attempted to defend the use of "n/a" in Table 1A by testifying that there was "no way" to "correct mathematically" for the LT 20 values to calculate an average at the one-month timepoint for the 45-liter batches, and that there is "no good way of handling the data when you don't have reportable numbers for some of your data points." JTX-4289.25-26, 38-39 (Los Tr. 127:18-20, 127:22-24, 128:22-129:7, 129:11-16, 168:19-169:19); DTX-2176.30. However, Ms. Los understood that it would have been possible to report individual batch values in the patent rather than an average. JTX-4289.26 (Los Tr. 129:17-19, 129:23).

503. Pacira's witnesses testified that it was Dr. Dai who ultimately drafted Table 1A, not Ms. Los. *Supra* Section III.D.2.a.(1). However, Ms. Los's testimony implies that Ms. Los was also complicit in the decision to use "n/a" for the one-month data in Table 1A, which was a false and misleading statement to the USPTO for the reasons discussed above. *Supra* Section III.C.2.a.(1). For the same reasons discussed above with respect to Dr. Dai, as well as the fact that Ms. Los used "NA" in the Los Spreadsheet to indicate that data was "not available," it is not plausible that Ms. Los was unaware that the use of "n/a" in Table 1A was false and misleading, and that it concealed the existence of anticipatory one-month data. *Supra* Section III.C.2.a.(2).

504. The single most reasonable inference is that Ms. Los was aware that the withheld data in the Los Spreadsheet was material to the patentability of at least claims 1, 3, and 5 of the '495 Patent (and that the Ardekani Data was material to the patentability of at least claims 1, 3, 5, and 7), and was aware this data had not been submitted to the USPTO. Nonetheless, Ms. Los agreed with Dr. Dai to report "n/a" in Table 1A for the average one-month erucic acid concentration, which Ms. Los knew to be the key limitation for assessing novelty of claim 1. The single most reasonable inference is that Ms. Los assisted Dr. Dai in falsely representing to the USPTO that no data existed at the one-month timepoint through the use of "n/a" in

Table 1A, knowing that this representation was false and misleading, and that it was material to the pending claims.

(3) Ms. Los Knowingly Withheld Additional Material Information in the Ardekani Data from the USPTO

505. As discussed above, Ms. Los compiled the 45-liter erucic acid data in the Los Spreadsheet from a larger collection of data, the Ardekani Data. *Supra* Section III.B.1. However, Ms. Los included only a subset of the Ardekani Data in the Los Spreadsheet—ten lots from Pacira's San Diego SCC facility. *Id.* Ms. Los excluded from the Los Spreadsheet the eight 45-liter Swindon lots in the Ardekani Data, which showed that claim 7 was anticipated (as well as claims 1, 3, and 5), and never provided this additional anticipatory data to the USPTO during prosecution. *Id.* The withheld 45-liter Swindon batch data in the Ardekani Data therefore went beyond the withheld data in the Los Spreadsheet—while the Los Spreadsheet only showed that claims 1, 3, and 5 were anticipated by 45-liter EXPAREL®, the withheld portions of the Ardekani Data showed that claim 7 was additionally anticipated. *Supra* Section III.B.2.

506. The single most reasonable inference is that Ms. Los was aware of the withheld portions of the Ardekani Data and knew that it was material to one or more claims of the '495 Patent, and knowingly withheld that material information from the USPTO.

507. According to Ms. Los and Dr. Ardekani, the Ardekani Data was requested and received from Pacira's regulatory and quality control groups in December 2020 as background information to inform the design of a planned stability study on EXPAREL® in prefilled syringes. JTX-4289.35-36 (Los Tr. 161:21-161:22, 161:25-162:5, 162:7-11, 162:25-163:06, 165:16-20); JTX-4287.13-15 (Ardekani Tr. 138:21-139:25, 140:9-17, 140:19-141:9). Ms. Los and Dr. Ardekani were both involved in the prefilled syringe stability study. JTX-4289.34-35 (Los Tr. 161:3-9, 161:11-16).

508. Ms. Los was in possession of all of the Ardekani Data, including the data showing that the Swindon batches met six-month erucic acid limitation as well as the one-month erucic acid limitation. Dr. Ardekani forwarded this data to Ms. Los when he obtained it. JTX-4287.22; 15 (Ardekani Tr. 142:19-143:8, 143:10-12); DTX-2465.1. Dr. Ardekani also compiled the erucic acid data from the Ardekani Data into a spreadsheet and provided that spreadsheet to Ms. Los. JTX-4287.3-4 (Ardekani Tr. 45:20-46:1, 46:3-5, 46:24-47:10, 47:17-48:1, 48:5). All of the Ardekani Data was therefore available to Ms. Los as of at least December 2020. JTX-4287.19 (Ardekani Tr. 158:2-4, 158:6).

509. Dr. Ardekani testified that he did not decide to withhold any of the Ardekani Data from the USPTO, and that he is unaware of any explanation or reason

as to why some of the Ardekani Data was omitted from the Los Spreadsheet. JTX-4287. 21 (Ardekani Tr. 228:3-5, 228:23-25, 229:17-20, 229:23).

510. The Los Spreadsheet contains annotations throughout indicating that its 45-liter data is limited to batches from the SCC manufacturing facility, in the data tables and figures. JTX-4037.18, 20-21, 28, 45. For instance, one version of Figure 3B is captioned "[Erucic] Acid in 200L vs 45L (SCC) during 25 °C Incubation." JTX-4037.21. However, in the patent itself, these annotations have been deleted. JTX-4121.08-09.

511. The single most reasonable inference is that despite the fact that Ms. Los had been provided with all of the Ardekani Data when she drafted the Los Spreadsheet, she decided not to include the eight 45-liter Swindon batches showing anticipation of claim 7.

512. As discussed above, Ms. Los was aware that the claims of the '495 Patent related to erucic acid concentration after storage at 25 °C for one, two, three, and six months—she reviewed the claims during prosecution, was able to interpret them at deposition, and submitted a declaration to the USPTO regarding the purportedly improved stability of the claimed product as measured over a period of six months. *Supra* Section I.C.2, Section III.D.2.b.(2). The single most reasonable inference is that Ms. Los recognized the materiality of the eight 45-liter Swindon

batches in the Ardekani Data when she chose to exclude them from the Los Spreadsheet, and to withhold that data from the USPTO during prosecution.

513. Ms. Los provided no plausible explanation for why she omitted the 45-liter Swindon data in the Ardekani Data from the Los Spreadsheet, and why it was never disclosed to the USPTO.

514. Prior to Ms. Los's deposition, Pacira stated in an Interrogatory response that the "reference sample" lots for Table 1A were chosen "because the 25°C stability study data at 1 month, 2 month, 3 month, and 6 month time points for these batches had been collected for a different study called the prefilled syringe stability study, and it was convenient to use the same lots." DTX-2176.29. Pacira further stated that "while there were 10 lots manufactured related to the prefilled syringe stability study, 3 of those lots did not yet have 25°C stability study data at the 6 month time point, so only 7 lots . . . were used to calculate the average" in Table 1A. *Id.*

515. When shown this Interrogatory response at deposition, Ms. Los endorsed Pacira's explanation that it was "convenient to use the same lots for the erucic acid stability data in Table 1A of the '495 Patent and the prefilled syringe stability study," (*id.*) because the data gathered for the prefilled syringe study "met minimum criteria for a number of data points with measurable erucic acid," which

was "the same criteria . . . needed to make the comparison for Table 1A." (JTX-4289.36 (Los Tr. 165:3-15)).

516. However, Pacira's Interrogatory response and Ms. Los's testimony are inconsistent with Ms. Los's decision to omit the 45-liter Swindon batches in the Ardekani Data from the Los Spreadsheet. The "25°C stability study data at 1 month, 2 month, 3 month, and 6 month time points" had also been collected for the 45-liter Swindon batches in connection with the prefilled syringe study—indeed, it was part of the same set of data that Ms. Los used to generate the Los Spreadsheet. DTX-2176.29; *supra* ¶ 305. The 45-liter Swindon batches in the Ardekani Data had full data for one, two, three, and six months at 25 °C, and therefore "met minimum criteria for a number of data points with measurable erucic acid" at least as much as the batches that Ms. Los included in the Los Spreadsheet. JTX-4287.16-19 (Ardekani Tr. 147:22-148:12, 148:15-16, 148:22-23, 148:25-149:3, 149:5-8, 149:11-14, 149:19-20, 149:21-24, 150:23-151:4, 151:6-16, 151:17-23, 152:1-6, 152:8, 152:13-14, 152:16-153:3, 153:7-8, 153:19-22, 154:2, 154:11-12, 154:13, 154:20-22, 154:24); Tr. 431:4-9, 431:25-435:3 (Schwendeman); DTX-2465.3, 5, 7, 9, 11, 13, 15, 17, 19. In fact, the omitted 45-liter Swindon batches had ***more*** available data than three of the SCC lots included on the Los Spreadsheet (lots 20-3066, 20-3067, and 20-4076), which were included in the Los Spreadsheet despite

lacking six-month measurements of erucic acid. JTX-4037.18; JTX-4289.23 (Los Tr. 124:11-22, 124:24).

517. At trial, Pacira argued that Pacira's unsold batches (including the 45-liter Swindon batches in the Ardekani Data) were not necessarily representative of the properties of prior art EXPAREL®. As explained above, this argument is incorrect. *Supra* Section II.A.4. To the extent that Pacira argues that this distinction may have been a motivating factor in Ms. Los's decision not to disclose the anticipatory Swindon batches in the Ardekani Data, such an argument is contradicted by the record. As explained below, Ms. Los testified that it made no difference to her analysis which of Pacira's 45-liter batches were sold and which were not, as she understood that the stability data in Pacira's regulatory submissions reflected the properties of commercial 45-liter EXPAREL® (whether or not each batch in those submissions was itself sold commercially).

518. Ms. Los testified that she understood that the data received from Pacira's regulatory group for the prefilled syringe study was part of an "annual stability report," and that she believed that the stability data submitted to FDA in Pacira's annual reports was representative of the properties of the commercial product. JTX-4289.37 (Los Tr. 165:21-24, 166:01-21, 166:23). The withheld 45-liter Swindon data in the Ardekani Data was included in the same set of annual report submissions that Ms. Los received from Pacira's regulatory group. *Supra* ¶ 308.

519. Ms. Los did not know whether any of the 45-liter batches in the Los Spreadsheet were commercial batches, and it did not matter for the purposes of her comparison. JTX-4289.23 (Los Tr. 124.25-125:18) ("We were working with the stability data that we were provided from regulatory, and we didn't discriminate between them."). In fact, Ms. Los included a combination of data for sold and unsold batches in the Los Spreadsheet, and characterized all of this data in the '495 patent as representing the prior art "commercial Exparel® product." JTX-4121 (13:49-55); *supra* ¶ 302. She believed that the data she received from Pacira's regulatory group were "representative of what the values would be for commercial batches." JTX-4289.23-24 (Los Tr. 125:13-125:18). Indeed, seven of the eight 45-liter Swindon batches were registration batches (DTX-2465.3), and Ms. Los specifically testified that she understood registration lots to be representative of the properties of commercial lots. JTX-4289.21 (Los Tr. 120:24-121:6, 121:9). Her understanding is that "any batch or series of batches should be representative of the . . . process as a whole," albeit with "some scatter around some of the measurements." JTX-4289.40 (Los Tr. 184:24-185:04, 185:6-9).

520. As discussed above, Ms. Los understood that the claims of the '495 Patent required specific erucic acid concentrations at specific timepoints, including at the six-month timepoint, and that the claimed erucic acid concentration was a key aspect of purported novelty. During prosecution, Ms. Los also submitted a

Declaration explicitly arguing for the novelty of the claims on the basis of the erucic acid limitation, confirming Ms. Los's knowledge that this limitation was key to patentability. *Supra* Section I.C.2.

521. The single most reasonable inference is that Ms. Los was in possession of the anticipatory 45-liter Swindon data in the Ardekani Data, knew that it was material to one or more pending claims, and intentionally withheld that information from the USPTO during prosecution of the '495 Patent.

(4) Ms. Los Knowingly Made False and Misleading Statements Regarding "Improved Stability" and "Higher" Bupivacaine Concentration

522. As discussed above, Ms. Los represented to the Examiner in the Los Declaration that the claimed product had "superior stability," and implied that it had a "higher" concentration of bupivacaine, as compared to prior-art EXPAREL®. *Supra* Section I.C.2. These false and misleading representations were instrumental in obtaining allowance of the '495 Patent. *Id.* For at least the reasons below, the single most reasonable inference is that Ms. Los was aware that these statements were false and misleading when she made these representations to the USPTO.

523. Ms. Los signed her declaration to the USPTO on April 21, 2021, and understood that any false statements to the USPTO in her declaration could jeopardize the validity of any resulting patent. JTX-4289.46-47 (Los Tr. 213:23-214:03, 214:05-215:09). As reflected in her declaration, Ms. Los confirmed at

deposition that she was "familiar with the content and prosecution history" of the application for the '495 Patent when she submitted her declaration, "including the currently amended claims." JTX-4289.47 (Los Tr. 215:10-12, 215:13-23); JTX-4001.2175.

524. Prior to Ms. Los's submission of her declaration, the Examiner had rejected all pending claims as obvious over Camu and Li. JTX-4289.44 (Los Tr. 207:1-121, 208:16-21, 209:15-24); *supra* ¶ 26. The pending claims included claim 1—the only independent claim, with the one-month erucic acid limitation—as well as claims 3, 5, and 7, with erucic acid limitations at subsequent timepoints. *Supra* Section I.C.2.

525. In response, Dr. Dai had argued to the Examiner that the claims were novel based on the one-month erucic acid limitation and purportedly "higher concentrations of bupivacaine," and had amended the claims to require the purportedly "higher concentrations" of bupivacaine. JTX-4289.45 (Los Tr. 210:8-10, 210:11-13, 210:17-211:18, 212:1-5, 212:20-213:4); *supra* ¶ 28. Additionally, the Examiner had specifically requested "a declaration of why one skilled in the art would not expect the prior art to have the same claimed acid concentration"—i.e., the one-month limitation for claim 1 and all dependent claims, with additional timepoints for a few dependent claims. JTX-4289.46 (Los Tr. 212:21-213:4); *supra* ¶ 28

526. With respect to the concentration of bupivacaine, Ms. Los stated in her Declaration that the claimed MVLs had a target concentration of bupivacaine "from about 12.6 mg/mL to about 17.0 mg/mL," and explicitly argued that the claims were novel based in part on that limitation. Tr. 648:22-649:23 (Slifer); JTX-4001.2179-80. When Ms. Los submitted her declaration, she was aware that there was no difference in bupivacaine concentration between 200-liter and 45-liter batches of EXPAREL®. JTX-4289.18, 46 (Los Tr. 89:17-20, 89:23-24, 212:13-16). However, neither Dr. Dai nor Ms. Los informed the Examiner that the claimed bupivacaine concentration was the same as prior-art EXPAREL® in their communications during prosecution. *Supra* Section III.C.2.c.

527. While Ms. Los's statement regarding the concentration of bupivacaine was factually accurate in isolation, it was incomplete and misleading in context, particularly in view of Dr. Dai's representation that this concentration was "higher" than the prior art and a ground for novelty. *Supra* Section I.C.2. Ms. Los was familiar with the claims and prosecution history when she signed her Declaration, including the reasons for which her statement regarding bupivacaine concentration was incomplete and misleading, and relied on the bupivacaine concentration herself to argue for novelty in the same Declaration. Tr. 648:22-649:23 (Slifer); JTX-4001.2178-80; JTX-4289.47-48 (Los Tr. 215:10-12, 215:13-23).

528. The single most reasonable inference is that Ms. Los was aware that her statement regarding bupivacaine concentration was incomplete and misleading when she submitted it to the USPTO.

529. In the Los Declaration, Ms. Los also represented to the Examiner that Pacira's 200-liter process "yield[ed] a bupivacaine MVL composition with superior stability as compared to the product made by the prior process," because it had "demonstrated less lipid membrane degradation, by measuring . . . erucic acid . . . over a period of 6 months at 25 °C." JTX-4001.2179. In the same paragraph, Ms. Los noted that the claimed product was "expected to have a shelf life of up to 2 years when properly handled and stored at 5°C," implying in context that this shelf life represented "superior stability." *Id.*

530. Ms. Los understood that a shelf life of "up to 2 years when stored at 2-8 °C" was not new for the 200-liter process, and therefore did not illustrate "improved stability," but did not mention in her declaration that this shelf life was the same as prior-art EXPAREL®. JTX-4289.18 (Los Tr. 90:5-7, 90:11); Tr. 648:8-21 (Slifer); JTX-4001.2178-79.

531. As discussed above, Ms. Los's statement in her declaration regarding "superior stability" would have been understood in context to refer to the one-month erucic acid limitation in claim 1, as well as the subsequent timepoints in claims 3, 5, and 7, and was objectively false and misleading. *Supra* Section III.C.2.b.(1). For at

least the reasons below, the single most reasonable inference is that Ms. Los knew that her statements to the USPTO regarding purportedly "superior stability" were false and misleading.

532. **First**, as discussed above, Ms. Los was in possession of data showing that claims 1, 3, 5, and 7 were anticipated when she filed her declaration (the Los Spreadsheet and the Ardekani Data), and that the claimed erucic acid levels were not novel at any timepoint. *Supra* Section III.B.1-2, Section III.C.1.a-b.

533. **Second**, as discussed above, Ms. Los was aware when she filed her declaration that Pacira had affirmatively concealed the anticipatory one-month data in the Los Spreadsheet through the use of "n/a" in Table 1A. *Supra* Section III.C.2.a. When Ms. Los submitted her declaration, the single most reasonable inference is that she knew her statement regarding "superior stability" would be interpreted in context to refer to all timepoints, including the one-month timepoint. When Ms. Los submitted her declaration, claim 1 of the '495 Patent only related to the one-month erucic acid concentration. *Supra* ¶ 32. Ms. Los understood that claim 1 of the '495 Patent only related to the one-month erucic acid concentration. JTX-4289.49 (Los Tr. 218-18-20). The file history, which Ms. Los was familiar with when she filed her declaration, also made it clear that the primary focus of the discussion between Dr. Dai and the Examiner was claim 1 and the one-month limitation. Section I.C.2; JTX-4289.47 (Los Tr. 215:10-12, 215:13-23).

534. This inference is corroborated by the fact that Ms. Los testified that she understood similar statements to "improved stability" in the specification of the '495 Patent to refer to the erucic acid concentrations reported and claimed in the patent, specifically including the one-month erucic acid limitation in claim 1. Ms. Los understood the statements regarding "improved stability over the commercial EXPAREL product" in the specification of the '495 Patent to refer to the erucic acid stability data presented in the patent. JTX-4289.13 (Los Tr. 74:18-75:5, 75:8); JTX-4121.16 (13:49-51). More specifically, Ms. Los understood that the reference to "improved stability" in the specification referred to "the erucic acid concentration of the 200-liter material," including the one-month concentration in Claim 1. JTX-4289.15 (Los Tr. 80:12-15, 80:19-20).

535. When Ms. Los made her statements about "superior stability" to the USPTO, she "was aware at the one-month time point that some of the 45-liter lots had erucic acid levels less than 20, which is lower than the number reported in [claim 1.]" JTX-4289.49 (Los Tr. 218:23-219:13).

536. When confronted with her statements to the USPTO, Ms. Los offered the excuse that she understood her statements regarding stability as relating to "the hydrolysis rate over time," "not an absolute number at an early time point." JTX-4289.48-49 (Los Tr. 216:12-15, 216:23-25, 218:23-219:2, 219:6-13).

537. This excuse is not credible. As discussed above, it would have made no procedural sense for Pacira to submit an inventor declaration directed to "the hydrolysis rate over time," in view of the pending claims and previous discussions with the Examiner. *Supra* Section III.C.2.b.(1)-(2). In addition, this excuse is contradicted by Ms. Los's own testimony, as discussed below.

538. As discussed above, Ms. Los understood that claim 1 had a limitation directed to the one-month concentration of erucic acid, not "the hydrolysis rate over time." *Supra* Section I.C.2. She understood that the one-month erucic acid limitation in claim 1 was the critical limitation for the purpose of assessing novelty, and was familiar with the prosecution history and claims when she submitted her declaration. JTX-4289.47 (Los Tr. 215:10-12, 215:13-23); JTX-4001.2175.

539. Ms. Los confirmed that she understood similar statements in the specification regarding "improved stability" as referring to the one-month erucic acid concentration in claim 1. JTX-4289.15 (Los Tr. 80:12-15, 80:19-20).

540. At best, even if Ms. Los believed that her statement regarding "superior stability" referred to "the hydrolysis rate over time" in her own mind (which the evidence suggests she did not), the single most reasonable inference is that Ms. Los knew and intended that her statement would be read by the Examiner as implying lower concentrations of erucic acid at the one-, two-, three-, and six-month timepoints.

541. **Third**, Ms. Los was aware when she made her statements regarding purported "superior stability" that there was no practical significance to the small changes in erucic acid reported in the '495 Patent, even for the differences reported at the six-month timepoint.

542. As discussed above, Ms. Los was aware that 200-liter EXPAREL® and 45-liter EXPAREL® had the same two-year refrigerated shelf life, and mentioned this shelf-life in her Declaration (while omitting the fact that it was the same for both products). *Supra* Section III.C.2.b.(1)-(2).

543. Ms. Los was aware that EXPAREL® was stored at 2-8 °C, and that 25 °C was not the recommended storage temperature for EXPAREL®. JTX-4289.33 (Los Tr. 157:12-13, 157:16-19, 157:22). She was also aware that as of January 2021, the 200-liter batches reported in the '495 Patent had been tested for stability at 5 °C, but the level of erucic acid in those batches was so low that it could not be measured. JTX-4289.33 (Los Tr. 158:11-16, 158:18-24).

544. Ms. Los does not know whether or not the 200-liter product is noticeably more stable than the 45-liter product under normal storage conditions. JTX-4289.34 (Los Tr. 159:5-6, 159:10, 159:18-20, 160:5-9, 160:12).

545. Ms. Los and her team did not perform any statistical calculations on the erucic acid data to see if there was a statistical difference between the 200-liter and 45-liter batches that they measured. Los testified that she could not recall any reason

why such calculations were not performed. JTX-4289.32 (Los Tr. 155:3-6, 155:8-9, 155:15-16).

546. Over her tenure at Pacira, Ms. Los periodically received and reviewed stability data for prior art 45-liter EXPAREL®, including data for multiple batches with erucic acid less than about 23 µg/mL after one month and/or less than about 99 µg/mL after six months. JTX-4289.58-61 (Los Tr. 256:19-257:10, 258:20-259:5, 259:10-20, 259:22-260:6, 260:8-9, 260:17-25, 261:25-262:3, 262:11-14, 262:25-263:5, 264:3-264:24, 266:1-9); DTX-2481.1, DTX-2482.15-19 (including batches 13-2204, 13-2205, and 13-2206 at page 18); JTX-4086.1, JTX-4084.32. This data also showed that after 24 months of storage at 5 °C, none of the batches of 45-liter EXPAREL from Pacira's commercial facilities had more than about 40 µg/mL of erucic acid. DTX-2482.2-8.

547. The historical data that Ms. Los had previously received and reviewed was consistent with the data in the Los Spreadsheet and the Ardekani Data: the claimed ranges of erucic acid in claims 1, 3, 5, and 7 of the '495 Patent were not novel compared to 45-liter EXPAREL®, and the six-month erucic acid concentration after storage at 25 °C was not predictive of the erucic acid level within a two-year refrigerated shelf life (which remained much lower).

548. Based on the stability data that Ms. Los had reviewed over the years (including this older data and the data in the Los Spreadsheet and Ardekani Data),

there was no plausible basis for her to believe that the 200-liter erucic acid levels reported in the '495 Patent were novel at any time point, or that they would translate to any meaningful stability difference under normal refrigerated conditions.

549. Additionally, Ms. Los was aware when she submitted her Declaration that the 200-liter registration lots in the '495 Patent were actually having problems with stability, rather than having "superior stability." As of at least October 13, 2020, Ms. Los was aware that the 200-liter registration lots were in danger of failing to meet stability criteria for d_{90} particle size. JTX-4289.51 (Los Tr. 222:2-13, 222:14-16, 222:17-223:7); JTX-4108.1.

550. Moreover, Ms. Los was aware that the small changes in erucic acid reported in the '495 Patent would have no practical impact on the properties of the product, even if the six-month values at 25 °C were predictive of erucic acid during a two-year refrigerated shelf life (which they were not).

551. As of at least 2014, Ms. Los has been aware that the shelf-life specification for erucic acid in EXPAREL is no more than 310 µg/mL, and that degradation at that level would not be expected to have any impact on EXPAREL's product attributes. JTX-4289.64-66 (Los Tr. 284:15-23, 285:1-14, 285:18-23, 285:25-286:3, 288:13-289:1, 289:4-289:11, 289:15-289:20, 289:24-25); DTX-2438.1; DTX-2437.1. Ms. Los included the specification of NMT 310 µg/mL in the Los Spreadsheet itself, showing her continued awareness. JTX-4287.7-8 (Ardekani

Tr. 87:19-23, 91:4-15, 91:18-20); JTX-4037.18. Ms. Los understood that the change in erucic acid levels reported in the '495 Patent would not be expected to have any practical impact on EXPAREL's other product attributes over its two-year refrigerated shelf life. JTX-4289.66 (Los Tr. 290:1-4, 290:8-13).

552. In view of Ms. Los's awareness of this specification, there is no plausible basis for Ms. Los to have believed that the small differences in erucic acid concentrations reported in the patent had any practical impact that would constitute "improved stability."

553. For at least the reasons above, the single most reasonable inference is that Ms. Los made her statements regarding "improved stability" and bupivacaine concentration to the USPTO with the knowledge that those statements were false and misleading.

(5) The Single Most Reasonable Inference is that Ms. Los Acted with the Intent to Deceive the USPTO

554. The single most reasonable inference is that Ms. Los knowingly withheld material information from the USPTO during prosecution and knowingly made false and misleading statements to the Examiner with the intent to deceive the USPTO. Each of Ms. Los's instances of misconduct went directly to key issues during prosecution, and were instrumental in obtaining issuance of the '495 Patent. *Supra* Section I.C.2. Standing alone, each instance would be an egregious violation

of the duty of candor, and the single most reasonable inference for each instance of misconduct is that Ms. Los intended to deceive the USPTO. As a whole, Ms. Los's pattern of conduct is even more egregious, showing a sustained pattern of targeted deception calculated to mislead the Examiner into allowing the claims of the '495 Patent.

555. As of late 2020, Ms. Los was aware that Pacira desperately needed a new Orange Book patent before its existing Orange Book patent expired at the end of 2021, to block generic competition for EXPAREL® (the company's most important product). *Supra* Section III.D.2.b.(1).

556. During prosecution of the '495 Patent, Ms. Los was aware that Pacira's arguments for novelty were based on (1) the erucic acid limitations of claims 1, 3, 5, and 7 (particularly the one-month limitation of claim 1) and (2) the purportedly "higher" concentration of bupivacaine. *Supra* Section I.C.2.

557. Ms. Los was aware of her ethical obligation during prosecution to disclose material information, as well as to be honest with the Examiner and not to mislead him. *Supra* Section III.D.2.b(1). She was also aware that Pacira's internal data on 45-liter EXPAREL® was the type of information that would be relevant to the patentability of the claims. *Supra* Section III.D.2.b(2).

558. Ms. Los was aware that the data underlying the patent itself, in the Los Spreadsheet, showed that at least claims 1, 3, and 5 of the '495 Patent were

anticipated by prior art 45-liter EXPAREL®. *Supra* Section III.B.1-2. She was also aware that this anticipatory data had never been shared with the USPTO. *Supra* Section III.D.2.b.(2). Rather than disclosing this anticipatory data to the USPTO, Ms. Los assisted Dr. Dai in concealing its existence, through the false and misleading use of "n/a" in Table 1A. *Id.*

559. Ms. Los was also in possession of the Ardekani Data, which additionally showed that Claim 7 was anticipated and the six-month erucic acid limitation was not novel. *Supra* Section III.B.2. Ms. Los excluded this anticipatory data from the Los Spreadsheet, and never provided it to the USPTO during prosecution of the '495 Patent. *Supra* Section III.C.1.b, Section III.D.2.b.(3).

560. To obtain issuance of the '495 Patent, Ms. Los submitted her Declaration, which falsely stated that the claimed product in the '495 Patent had "superior stability" compared to 45-liter EXPAREL®, and misleadingly highlighted its bupivacaine concentration as a purported point of novelty. *Supra* Section I.C.2. Ms. Los knew (and intended) that her Declaration would be used to convince the Examiner that the claimed product was novel based on the claimed concentrations of erucic acid (most importantly, at the one-month timepoint in claim 1), and based on the purportedly higher concentration of bupivacaine. *Supra* Section III.D.2.b.(4). Ms. Los knew that her affirmative statements to the Examiner were false and misleading, and knew that these properties were not actually novel compared to prior

art 45-liter EXPAREL® (as would have been revealed by the undisclosed material information in her possession). *Supra* Section III.D.2.b.(4).

561. There is no plausible explanation for Ms. Los's withholding and concealment of anticipatory data from the USPTO or her false and misleading statements, other than an intent to deceive the USPTO into allowing the '495 Patent. Taken as a whole, her pattern of conduct throughout prosecution of the '495 Patent and related patents shows a consistent, coordinated attempt to conceal key prior art and mislead the USPTO. The single most reasonable inference is that Ms. Los engaged in each of her acts of prosecution misconduct with the intent to deceive the USPTO.

3. Additional Evidence of Deceptive Intent

a. Pattern of Deceptive Conduct During Prosecution of Related Patents

562. In addition to the '495 Patent, Pacira obtained several additional patents that share substantially the same specification: U.S. Patent No. 11,179,336 ("the '336 Patent") (JTX-4126), U.S. Patent No. 11,278,494 ("the '494 Patent) (JTX-4130); U.S. Patent No. 11,185,506 ("the '506 patent") (JTX-4128); U.S. Patent No. 11,304,904 ("the '904 Patent") (JTX-4131); U.S. Patent No. 11,311,486 ("the '486 Patent") (JTX-4133); U.S. Patent No. 11,357,727 ("the '727 Patent"); U.S. Patent No. 11,426,348 ("the '348 Patent") (DTX-2152); and U.S. Patent No. 11,452,691 ("the '691 Patent") (JTX-4140). Each of these patents contains the same information

on Example 1 and Table 1A as the specification of the '495 and '336 Patents, with certain changes noted below. Tr. 659:8-13 (Slifer).

563. The '336 patent, '494 patent, and '506 patent all contain claims to compositions with the same one-month erucic acid limitation as the '495 patent. Tr. 656:19-657:7 (Slifer); JTX-4121.20-21; JTX-4126.23; JTX-4130.22; JTX-4128.21-22. The '904 patent, '486 patent, '727 patent, '348 patent, and '691 patent do not contain the one-month erucic acid limitation. Tr. 657:19-658:7 (Slifer); JTX-4131.21-22; JTX-4133.21-22; JTX-4009.22-23; DTX-2152.22-24; JTX-4140.20-22.

564. Some of Pacira's related patents contain an added footnote under Table 1A stating:

> n/a: At the 1 month time point, several batches of the reference samples contained erucic acid at concentrations below the lower limit of detection of the assay (20 µg/mL). Therefore, an average value of erucic acid concentration for all batches of the reference samples could not be calculated at the 1 month time point.

Tr. 658:15-25 (Slifer); DTX-2152.21-22. Specifically, all of Pacira's related patents with the one-month erucic acid limitation lack the additional footnote under Table 1A explaining that some 45-liter batches of EXPAREL had less than 20 µg/mL of erucic acid at the one-month timepoint. Tr. 660:11-22 (Slifer); JTX-4121.19-21; JTX-4126.22-23; JTX-4130.21-22; JTX-4128.20-22. All of Pacira's related patents ***without*** the one-month erucic acid limitation do have the additional footnote under Table 1A. Tr. 660:11-22 (Slifer); JTX-4131.20-22; JTX-4133.20-

22; JTX-4009.21-23; DTX-2152.21-24; JTX-4140.19-22. This pattern was summarized by Mr. Slifer in DDX-4.10:

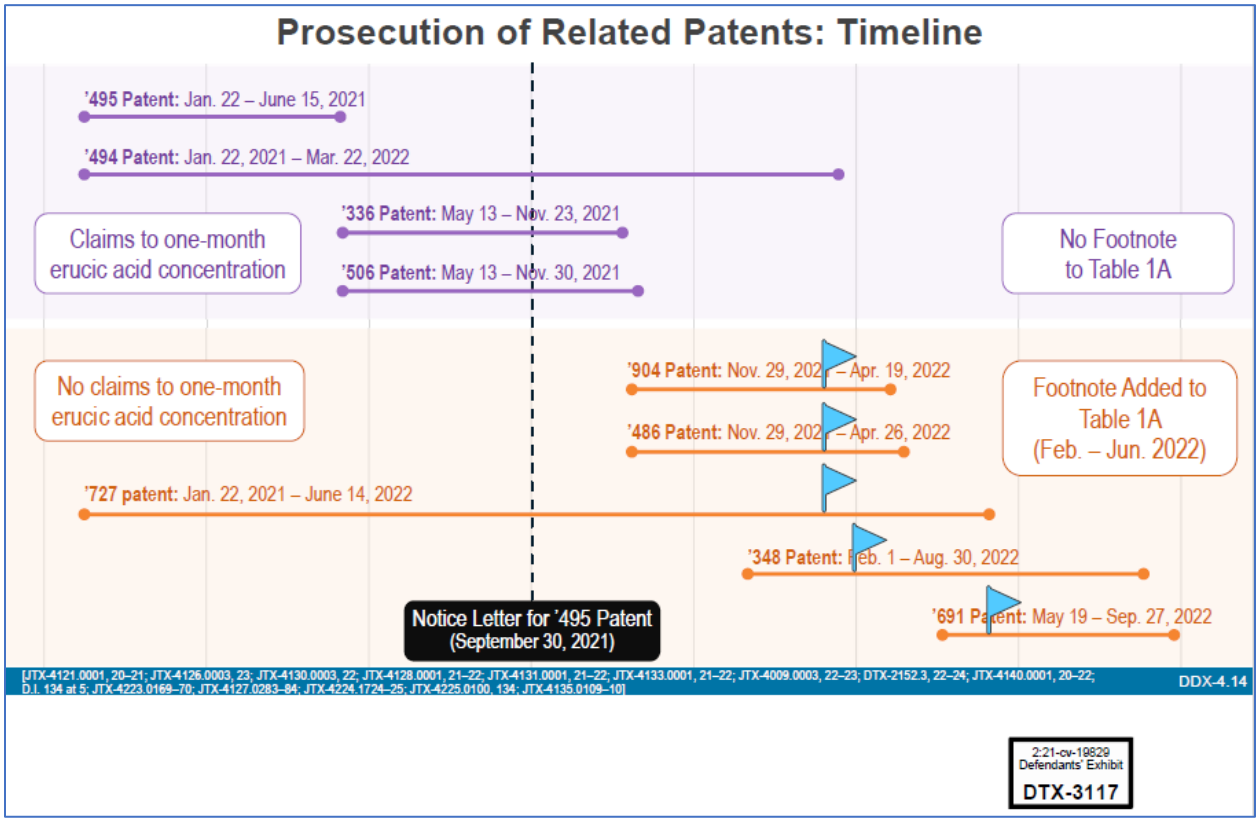
Patent / Application		One-Month Erucic Acid Limitation?	Footnote to Table 1A?
11,033,495 ('495 patent)	(JTX-4121)	YES	NO
11,179,336 ('336 patent)	(JTX-4126)	YES	NO
11,278,494 ('494 patent)	(JTX-4130)	YES	NO
11,185,506 ('506 patent)	(JTX-4128)	YES	NO
11,304,904 ('904 patent)	(JTX-4131)	NO	YES
11,311,486 ('486 patent)	(JTX-4133)	NO	YES
11,357,727 ('727 patent)	(JTX-4009)	NO	YES
11,426,348 ('348 patent)	(DTX-2152)	NO	YES
11,452,691 ('691 patent)	(JTX-4140)	NO	YES

DDX-4.10 (citing JTX-4121.19-21; JTX-4126.22-23; JTX-4130.21-22; JTX-4128.20-22; JTX-4131.20-22; JTX-4133.20-22; JTX-4009.21-23; DTX-2152.21-24; JTX-4140.19-22).

565. Dr. Dai supervised the drafting of the footnote added beneath underneath Table 1A in Pacira's related patents that lacked the one-month erucic acid limitation. JTX-4288.24 (Dai Tr. 235:25-236:13, 236:17-20); JTX-4133.20.

566. Pacira received the Notice Letter regarding the '495 Patent from Defendant Jiangsu Hengrui on September 30, 2021. After receiving the Notice Letter, Pacira stopped filing any new applications with one-month erucic acid claims, and started adding the footnote under Table 1A to some (but not all) of its pending applications. Tr. 662:6-663:1 (Slifer); DTX-3117.

567. When Pacira received the Notice Letter on September 30, 2021, it had three pending applications with one-month claims: the '494 patent, the '336 patent, and the '506 patent. DTX-3117. The '336 patent and the '506 patent issued on November 23, 2021 and November 30, 2021, without any footnote added to Table 1A. *Id.* A few months after those two patents issued, in February 2022, Pacira began adding the footnote to Table 1A. *Id.* This timeline is summarized in DTX-3117:



DTX-3117.1.

568. As of February 2022, Pacira had five pending patent applications. Tr. 663:9-664:15 (Slifer); DTX-3118. Two applications were pending before Examiner Jeffrey Washville: the '904 patent and '486 patent, both without the one-month

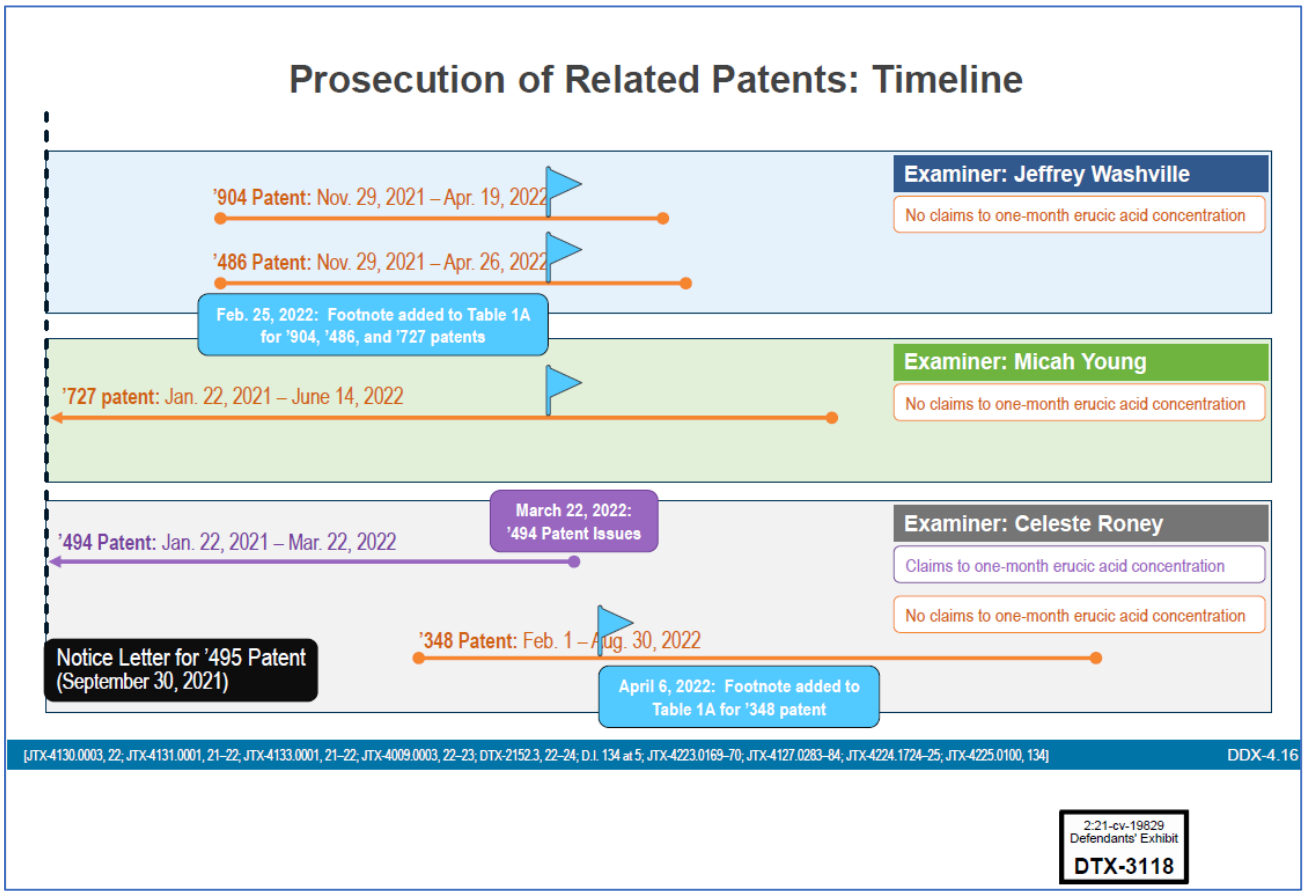
limitation. Tr. 663:9-664:15 (Slifer); DTX-3118. One application was pending before Examiner Micah Young: the '727 patent, also without the one-month limitation. Tr. 663:9-664:15 (Slifer); DTX-3118. Two applications were pending before Examiner Celeste Roney: the '494 patent, which did have the one-month limitation, and the '348 patent, which did not. Tr. 663:9-664:15 (Slifer); DTX-3118.

569. On February 25, 2022, Pacira added the footnote under Table 1A to the three applications pending before Examiners Washville and Young, none of which had the one-month limitation. Tr. 664:16-665:19 (Slifer); DTX-3118. Pacira did not add the footnote to either of the applications pending before Examiner Roney, one of which did have the one-month limitation. Tr. 664:16-665:19 (Slifer); DTX-3118. There was no procedural reason for Pacira to avoid adding the footnote to the applications pending before Examiner Roney at the same time as its other applications. Tr. 664:16-665:19 (Slifer); DTX-3118.

570. On March 22, 2022, the '494 patent issued, without the footnote under Table 1A. Tr. 665:20-666:21 (Slifer); DTX-3118. At that point, there were no more applications with the one-month limitation pending before Examiner Roney. Tr. 665:20-666:21 (Slifer); DTX-3118. Approximately two weeks later, Pacira added the footnote to the '348 patent before Examiner Roney, which did not have the one-month limitation. Tr. 665:20-666:21 (Slifer); DTX-3118. There was no procedural

reason for Pacira to wait until the ’494 patent issued before adding the footnote to the ’348 patent. Tr. 665:20-666:21 (Slifer).

571. The timing of Pacira’s selective addition of the footnote to Table 1A is summarized in DTX-3118:



DTX-3118.1.

572. Mr. Godici initially testified that to for Pacira add the footnote under Table 1A for certain subsequent patents, the examiners must have determined that there was “no new matter” in the footnote, which he defined as meaning that there was nothing in the new footnote that was not “already part of the specification.” Tr. 830:8-831:4 (Godici). However, he admitted that some information added in the

footnote (e.g., that the lower limit of detection of Pacira's erucic acid assay was 20 µg/mL) was not present in the previous version of the specification. Tr. 854:22-855:24 (Godici).

573. If the footnote under Table 1A contained no new matter, there would have been no procedural reason why Pacira could not have added it to all of its related patents, rather than selectively adding it to only the patents with no one-month erucic acid limitations. Tr. 856:21-857:4 (Godici).

574. The single most reasonable inference from Pacira's pattern of conduct in these related applications is that Pacira was aware that the original version of Table 1A concealed the existence of anticipatory one-month data through its use of "n/a." Once Pacira received the Notice Letter regarding the '495 Patent and knew that this family of patents would likely be litigated, it attempted to reverse this misconduct in some of its future patents—but exclusively for the patents without one-month claims. As illustrated by the timeline above (DTX-3118), Pacira meticulously timed the addition of the footnote to avoid bringing it to the attention of any examiner while one-month claims were still pending before that examiner. Pacira's conduct illustrates that its prosecution misconduct was knowingly and intentionally deceptive, and that it was carefully planned.

b. Deceptive Testimony from Pacira's Witnesses

575. The testimony at trial from Pacira's two live inventor witnesses, Jeffrey Hall and Dr. Grigsby, further illustrates the inventor team's willingness to go beyond the boundaries of factual accuracy to protect the '495 Patent.

576. At trial, Mr. Hall initially testified that Pacira was pursuing two potential alternative manufacturing processes—the 200-liter scale-up, and the "spray process"—and that he purportedly had more confidence in the spray process, and "doubt" in the 200-liter scale-up. Tr. 95:13-96:10, 96:23-97:10 (Hall). During cross-examination, however, Mr. Hall admitted that he had previously testified at deposition that he "th[ought] the 200-liter was going to happen regardless of the spray," because it was "a lower-risk of capital and time than committing to a spray process," and that "the lower risk option was always going to be the 200-liter and the pie-in-the-sky was going to be spray." Tr. 116:6-20 (Hall).

577. At trial, Dr. Grigsby testified that the second emulsion step of Pacira's 200-liter process purportedly resulted in higher levels of internal lysine, and therefore a lower rate of erucic acid generation. Tr. 167:13-168:15 (Grigsby). This testimony contradicted testimony from named inventor Mr. Hall, who testified that he does not know whether stability is affected by the mixing speed, mixer diameter, or blade height in the second emulsion step of Pacira's manufacturing process. Tr. 122:16-24 (Hall). On cross-examination, Dr. Grigsby admitted that his contribution

to the patent related to the manufacturing process, not the data on erucic acid, internal pH, or internal lysine, and that his testimony was merely parroting the data on the face of the patent. Tr. 181:7-15, 182:8-10 (Grigsby). He also testified that he did not personally know anything about the internal lysine measurements reported in the patent, other than what appears on the face of the patent, including how precise the assay was, whether it was performed correctly, or whether the data reported in the patent was accurate. Tr. 188:6-189:17 (Grigsby). Dr. Grigsby admitted that the lysine data on the face of the patent did not match the lysine measurements that Pacira reported to FDA, but could not provide any explanation as to why the numbers did not match, or whether the internal lysine data on the face of the '495 Patent was accurate. Tr. 198:12-200:6 (Grigsby); JTX-4053.5; JTX-4121.20 (Table 2A).

578. At trial, Dr. Grigsby initially testified that although Pacira's submissions to FDA stated that EXPAREL® manufactured using the 200-liter process had equivalent stability to 45-liter batches, Pacira would never "go out of [their] way to highlight differences even if they [were] better," because "that's just not part of a submission." Tr. 176:10-178:11 (Grigsby); JTX-4053.2, 4. On cross-examination, Dr. Grigsby admitted that in previous FDA submissions related to new manufacturing facilities, Pacira had in fact highlighted lower levels of erucic acid after six months' storage at 25 °C, unlike in their submissions for the 200-liter manufacturing process. Tr. 201:7-203:18 (Grigsby); JTX-4241.2

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Respectfully submitted,

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